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A NEW APPARATUS FOR DIRECT CINEROENTGENOGRAPHY[1]

by

Åke S. Gidlund

The apparatus described in this paper is designed to be used for taking direct cinematographic roentgenograms on a discontinuously moving film. The film employed in this apparatus is 13 cm wide (size of photograph 13 cm × 18 cm), and the maximum length of the film is 5.5 m. The film has been supplied by A. B. Ceaverken, Strängnäs, Sweden, and by Gevaert Film, Belgium.

Figure 1 shows an exterior view of the apparatus. Attention is called to the built-in fluorescent screen (H), which is of great value since it permits a more accurate focussing of the object to be examined.

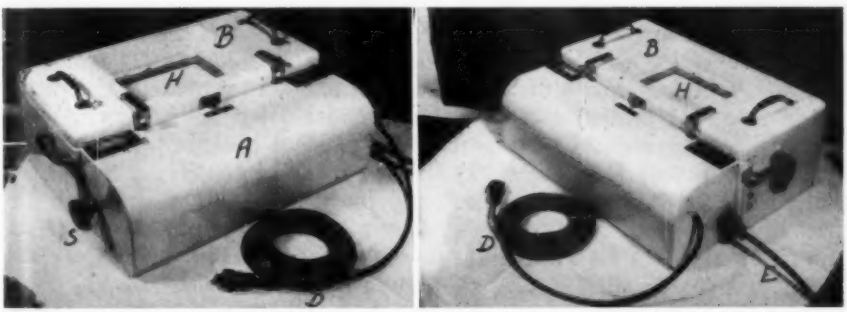

Fig. 1 a. Fig. 1 b.

Exterior view of cineroentgenographic apparatus. A: Protective cover for motor and gear. B: Removable lid of camera housing with fluorescent screen H. E: Two-core cable for motor circuit and exposure circuit. D: Cable and switch for remote control of exposure circuit. S: Knob for setting the number of photographs taken per second.

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From the Roentgen Department of the St. Eriks Hospital, Stockholm, Sweden (Head: Dr. C. SANDSTRÖM).

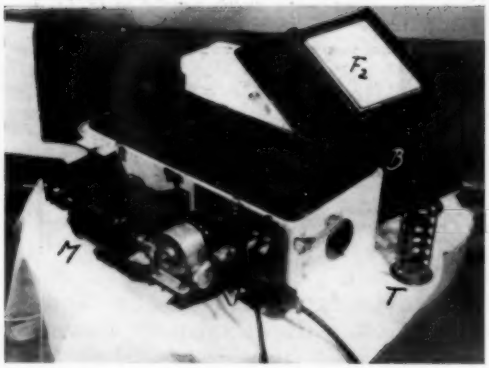


Fig. 2.

Fig. 3.

Fig. 2. View of cineroentgenographic apparatus after removal of lid and protective cover. B: Lid of camera housing with movable intensifying screen F_2. T: Film reel. M: A. C. motor.

Fig. 3. Insertion of film. F_1: Fixed intensifying screen. T: Film reel put in place and clamped.

Figure 2 represents the apparatus after removal of the lid and the protective cover which encloses the driving mechanism. The camera housing, which is made of a light-weight alloy, is provided with a lid (B in figures 1 and 2) attached to the housing by means of clamping devices, so that it can easily be removed and put back in place. A fixed fluorescent screen (H in figure 1) and a movable intensifying screen (F_2 in figure 2) are mounted in the lid. The joint between the lid and the lower part of the camera housing is sealed by means of a rubber gasket (U in figure 6) so as to be impervious to light. The interior of the camera housing is coated with black oxide and partly lined with lead, in order to prevent the passage of the roentgen rays. The bottom of the camera housing is provided with an opening, 13 cm × 18 cm in size, for the exposure of the film. The film is kept in close contact with an intensifying screen (F_1 in figure 3) fitted into this opening (further particulars are given below).

The film must be alternately fed at a great speed and brought to an instantaneous stop for exposure, and then it must be instaneously fed again. It is therefore necessary to reduce the inertia of the feeding mechanism as much as possible. For this reason, the film is not wound off a

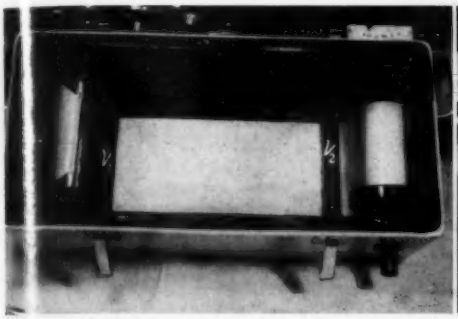


Fig. 4.

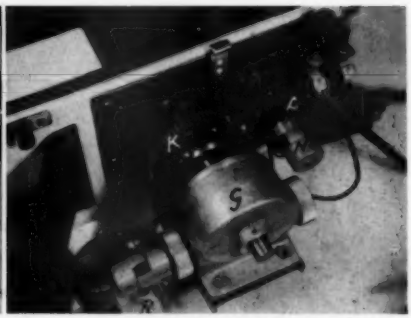


Fig. 5.

Fig. 4. Film inserted in apparatus. V_1 and V_2: Rollers keeping the film level on the fixed intensifying screen (F_1 in Fig. 3).

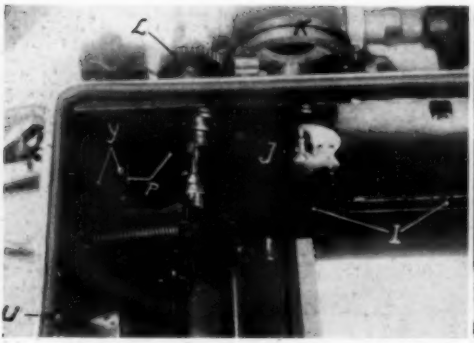
Fig. 5. Close-up of driving mechanism. G: Worm gear. R: Rheostat. K: Spur gear with toothed part visible. N: Rubber shock absorbers.

spool, which would have a relatively large mass. Instead, the film is rolled up and inserted between two dish-shaped bakelite disks which are provided with small rollers on the inside, in order to reduce friction. Before inserting the film, one of the bakelite disks is pulled aside by means of a knob (see figure 3). The film is kept level by two rollers (V_1 and V_2 in figure 4) which press it against the intensifying screen in the bottom opening of the camera housing.

The film is wound on a reel (T in figures 2 and 3, see also figure 4) which is perforated in order to reduce its mass, and thus its inertia, and is provided with a slot for fastening the film (see figure 4). The reel is attached to the shaft by means of two pins on the shaft fitting into the corresponding holes in the flange of the reel. The reel is clamped by the aid of a short spring, so that it can be removed easily and put in place.

The feeding mechanism is driven by a 220 volt alternating current motor (M in figure 2). The output of the motor can be controlled by means of a rheostat (R in figure 5). Since the speed of the motor is high, the motor is coupled to a worm gear (G in figure 5). The driven shaft of the worm gear carries a spur gear (K in figures 5 and 6), which on a part of its circumference has a gap free from teeth.

The film is fed by the spur gear which drives a pinion (L in figures 5 and 6) mounted direct on the shaft of the reel. When the toothed part of the spur gear has completed its revolution, and the tooth-free gap (K in figure 6) is turned towards the pinion (L in figure 6), then the pinion is no longer driven, with the result that the reel is brought to a stop and the motion of the film is therefore interrupted. When the spur



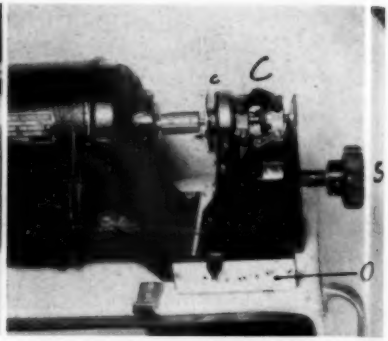


Fig. 6. Fig. 7.

Fig. 6. K: Tooth-free gap of spur gear (K in Fig. 5). L: Pinion driving film reel shaft. P: Revolving lever attached to film reel shaft, closing the switch Y in the exposure circuit. I: Metal bar for raising and lowering the movable intensifying screen (F_2 in Fig. 2) fitted in the lid of the camera housing. J: Cam for raising and lowering metal bar I, provided on either side of the bottom of the camera housing. U: Rubber gasket.

Fig. 7. C: Centrifugal speed governor with brake O. S: Knob for setting the number of photographs taken per second, which is indicated by the pointer on the scale O.

gear re-engages with the pinion, the reel is set in motion again, and the feed of the film is resumed, and so forth. The length of the toothed arc of the spur gear is adjusted to the gear ratio and to the diameter of the reel so that the film is fed 18 cm at a time (the size of each photograph is 13 cm × 18 cm). In order to ensure smooth engagement of the spur gear and the pinion during the transition from the toothed part of the spur gear and the pinion are provided with guide segments. The guide segment on the pinion is mounted by means of rubber shock absorbers (N in figure 5).

As soon as the film stops, it is exposed by means of a revolving lever (P in figure 6) attached to the shaft of the reel. This lever operates the spring contact of a switch (Y in figure 6) and thus closes the circuit. The switch is connected in the exposure circuit of the roentgen tube. The requisite time of exposure, as well as the voltage (in kilovolt) and the current (in milliampère) of the roentgen tube are set as usual. (Figure 6 illustrates the working of the mechanism at the instant of exposure.)

The driving mechanism described above cannot be used unless the speed of the motor is maintained constant. Since the load on the motor decreases when the film is stopped the speed of the motor otherwise would increase. For this purpose, a centrifugal speed governor of special design

Fig. 8. Case of cardiospasm. The roentgenograms are made half an hour after the administration of barium sulphate. Two pictures per second. Note almost standing peristaltic waves. (Cea film.)

(C in figure 7) is coupled directly to the motor shaft. This governor maintains the speed of the motor constant by means of automatically varied braking. The brake consists of a metal disk which is pressed against felt cushions (c in figure 7). The pressure exerted by the metal disk on the felt cushions, and hence also the number of photographs taken per second,

Fig. 9. Arteriography in a case of femoral artery occlusion with collaterals. Thr e pictures per second. (Gevaert film.)

can be varied by means of a knob (S in figure 7), and is indicated by a pointer on an empirically graduated scale (0 in figure 7).

The intensifying screen (F_2 in figure 2) fitted in the lid of the camera housing can be raised and lowered, and also slightly turned about its horizontal axes.

A metal bar (I in figure 6) held by a spring is provided on either side of the bottom of the camera housing. These bars are raised and lowered by means of a metal cam of special shape (J in figure 6) mounted on the shaft of the spur gear (K). When the lid of the camera housing is in place, two pins fitted on each side of the movable intensifying screen rest on the metal bars. When the film is to be fed, the metal bars, and hence the intensifying screen, are moved so as to eliminate friction between the film and the intensifying screens. As soon as the film is stopped for exposure, the bars, together with the intensifying screen, are lowered, so that the film is firmly held between this screen and the intensifying screen fitted in the bottom of the camera housing. This device helps to ensure that the film is quickly brought to a stop at the moment of exposure. (The pressure between the intensifying screens is relatively great since the movable screen is acted upon by springs.)

When the exposure to the roentgen tube is controlled by an ordinary mechanical interrupter, the maximum number of photographs that can be taken per second is 3.5. This number cannot be exceeded since the time is not sufficient to restore the mechanical interrupter to its initial position before the next radiogram must be exposed. Apart from the mechanical interrupter, the maximum number of photographs per second that can be taken by means of this apparatus is 5, on the assumption that the time of exposure is 0.1 sec.

Figures 8 and 9 are produced with the apparatus described. Figure 8 demonstrates a case of cardiospasm half an hour after the administration of barium sulphate and photographed with two exposures per second. The high rate of exposures made at constant intervals makes a close analysis of the peristalsis possible. The peristalsis in this case is not characterized by the usual type of proceeding transverse waves of contractions but by standing waves. (Further details on these particular problems will be published separately.) Figure 9 shows arteriography after injection of 4 ml Umbradil in the femoral artery. The technique allows a more accurate concept of vascular changes and circulation (1).

I am respectfully indebted to Director A. Wenner-Gren and the Wenner-Gren Foundation, Stockholm, for financial help with the present investigation.

The apparatus has been designed by the author in co-operation with AB Elema-Järnh., Stockholm, and manufactured by this company.

SUMMARY

A new apparatus for taking direct cinematographic roentgenograms on a discontinuously moving film is described. The size of each photograph is 13 cm × 18 cm. The maximum length of the film is 5.5 m.

ZUSAMMENFASSUNG

Es wird ein neuer Apparat beschrieben zur Aufnahme von Röntgenbildern auf einem ruckweise fortbewegten Film. Die Grösse jeder Aufnahme ist 13 × 18 cm. Die maximale Länge des Filmstreifens beträgt 5.5 m.

RÉSUMÉ

Description d'un nouvel appareil permettant de prendre des radiographies cinématographiques directes sur un film avec mouvement intermittent. Les photographies ont chacune 13 sur 18 cm. La longueur maximum du film est de 5.5 m.

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FROM THE RADIUM CENTRE FOR JUTLAND, AARHUS, AND THE MUNICIPAL HOSPITAL ROENTGEN DEPARTMENT, AARHUS, DENMARK (CHIEF: PROF. CARL KREBS, M D.)

THE RELATIONSHIP OF HAND-SCHÜLLER-CHRISTIAN'S DISEASE, LETTERER-SIWE'S DISEASE AND EOSINOPHILIC GRANULOMAS OF BONE[1]

(with report of five cases)

by

Poul Bjerre Hansen

During recent years the relationship between Hand-Schüller-Christian's Disease, Letterer-Siwe's Disease and Eosinophilic Granulomas of Bone has been the subject of heated discussion. There has been some diversity of opinion as to their pathogenesis, both in relation to each other and in general, and the discussion is still animated with contributions from practically all branches of the medical profession.

The delimitation of the first of these diseases, the *Hand-Schüller-Christian syndrome* with the three classical principal symptoms: defects of the cranial bones, exophthalmos and diabetes insipidus, took place about 1915—20 on the basis of publications by the three authors whose names have been attached to the disease. At that time it was believed to be due to a pituitary dysfunction (HAND (25—26), SCHÜLLER (42—43), CHRISTIAN (11)).

ROWLAND (41) (1928) was the first to describe the patho-anatomical essentials of the disease. He stated, that there was an accumulation of large, bright reticular cells and histiocytes, the so-called »foam cells», in a young connective tissue and reticular tissue infiltrated by a large number of lymphocytes and polynuclear leukocytes. ROWLAND demonstrated that the »foam cells» contained cholesterol, and for this reason the disease was regarded as a disturbance of the lipoid metabolism with hypercholesterolemia and a secondary storage of this substance in the reticulo-endothelial tissue with ensuing clinical manifestations. The

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disease was conceived to bear a certain relation to Gaucher's and Niemann-Pick's diseases.

During the following years it was realized that especially in the initial stage of the disease there were often only inflammatory or granulomatous patho-anatomical changes without accumulations of cholesterol in the reticulum cells. (CHESTER (9), CEELEN (8), LETTERER (34), GERSTEL (20).) The presence of giant cells and eosinophilic leucocytes in these granulomatous processes was emphasized by some pathologists, *e. g.* FRASER (18), and STRONG (46) mentioned the possibility that a close relationship with the reticuloses might exist (1936).

Finally, THANNHAUSER & MAGENDANTZ (48) showed in 1938 that the cholesterol-content of the blood was normal in Schüller-Christian's disease. To replace Rowland's theory of a general disturbance of the cholesterol metabolism THANNHAUSER (49) set forth the view in a comprehensive work (1940) that it was a disturbance of the intracellular lipoid metabolism in the reticulo-endothelial cells. The relationship with Gaucher's and Niemann-Pick's diseases, in which no specific lipemia could be demonstrated either, was maintained.

With regard to the clinical picture it was gradually realized that the syndrome established by CHRISTIAN was not constant, but only a comparatively frequent combination of symptoms (HENSCHEN (27), SOSMAN (45)). — The symptoms depend on the extent and localization of the xanthomatous processes and may vary to a very great degree. The disease may be encountered both in children and adults, but generally initiates in childhood and is little more frequent in boys than in girls. Some authors express the belief that it is a heredofamilial disorder. The prognosis is always serious, only one third of all cases surviving more than five years. Pre-eminently in adults one may encounter a protracted, sometimes fairly asymptomatic course of the disease, but as a rule there is often severe pituitary or cerebral dysfunction.

The second disorder, *Letterer-Siwe's disease*, was first described by LETTERER (33) in 1924. In 1933 SIWE (44) collected the reports published till that time, and set forth a number of criteria for the manifestations and course of the disease. The designation, Letterer-Siwe's disease, was introduced by ABT & DENENHOLZ (1) in a work on the subject from 1936.

The disease is pathologically characterized by a general hyperplasia of the reticulo-endothelial system with the development of localized tumour-like proliferations, especially in the spleen, liver, bone marrow, lymph nodes and the skin. Correspondingly, the symptoms are: swelling of the spleen, liver and lymph nodes, secondary anemia, a tendency to hemorrhagic diathesis and dermatitis, and in some cases destructive bone changes. The disease is found exclusively in children, most frequently under 2—3 years of age. The prognosis is always poor, the course

is acute, generally terminating fatally after a short time. The etiology is unknown, nor is it definitely known if it is a heredofamilial disorder.

SIWE described the disease as a specific, non-infectious reticulosis. This view was confirmed by WALLGREN (52) in a comprehensive work on the subject in 1940. However, WALLGREN regarded a separation into infectious and non-infectious reticuloses as doubtful, because these seriously affected children may easily contract some infectious disease. In addition, WALLGREN demonstrated an incipient accumulation of cholesterol in the reticular cells in some cases of Letterer-Siwe's disease. Based on these studies WALLGREN expressed the belief that Letterer-Siwe's disease should be regarded as an initial stage of Schüller-Christian's disease, but owing to the acute course this evolution would rarely manifest itself plainly. Hand-Schüller-Christian's disease was thus classified among the reticuloses. As already stated, also STRONG had mentioned this possibility, and the same holds good of FLORI & PARENTI (17).

The third group of diseases, *the eosinophilic bone-granulomas*, has been described as a distinct disease entity by LICHTENSTEIN & JAFFE (35) in 1940. According to these authors it was a localized, osteolytic bone lesion with a uniform histologic picture characterized by granuloma formation with accumulation of eosinophilic leucocytes, histiocytes and giant cells in a tissue chiefly consisting of reticular cells. The disease was encountered especially in late childhood and in adult life, had a benignant course and might be cured by irradiation as well as surgical therapy, and also sometimes spontaneously. Pre-eminently solitary, but also occasionally multiple bone foci were reported, sometimes occurring successively in different localities. The symptoms were swelling and tenderness of the affected bone. The etiology was obscure, but an infectious origin (virus?) was considered probable. In spite of thorough investigations OTANI & EHRLICH (40), who published seven similar cases at about the same time, could not demonstrate any infectious etiologic factor. (Subsequent investigations have also invariably proved negative, *e. g.* GREEN & FARBER (22).)

Since 1940 approximately 200 cases of this nature have been reported under the designation of eosinophilic granuloma of bone. The majority of these publications has come from North and South America and chiefly report benignant cases in adults. Among Scandinavian investigators dealing with the problem J. NIELSEN (39) and A. HØYER (28) may be mentioned.

However, very soon doubt arose as to whether it was warrantable to delimit the eosinophilic granulomas as a distinct entity. Several investigators were, independent of each other, led to believe that the eosinophilic bone granulomas are closely related to Schüller-Christian's disease. The American pathologists, FARBER (16) and GREEN & FARBER

(22—23) were the first to set forth this theory after extensive histologic investigations in 1942—44 of ten cases of eosinophilic granuloma, all in children. The Danish investigators, ENGELBRETH-HOLM, TEILUM & ERNA CHRISTENSEN (14) arrived at the same result in 1944. They base their opinion, that the eosinophilic granulomas and Schüller-Christian's disease must be regarded as different phases of the same disease entity, especially on histological, but also on clinical findings in five children suffering from eosinophilic disease. They distinguished between four phases: 1) A hyperplastic, proliferative reticulo-histiocytic phase, 2) A granulomatous phase with eosinophilic cells, macrophages and giant cells, 3) A xanthomatous phase dominated by the storage of lipoid represented by the »foam cells», and 4) A fibrous healing phase. — In a work on the differential diagnosis between the eosinophilic granulomas and Ewing's sarcomas in 1943 the Swedish research workers AHLSTRÖM & WELIN (2) mentioned the possibility of a close relation between these granulomas and the Schüller-Christian disease. In a comprehensive work on bone lesions from 1942 MALLORY (36) also touched on the problem and defended the relationship with Letterer-Siwe's disease demonstrated by WALLGREN.

In an additional work from 1944 JAFFE & LICHTENSTEIN (30) advocated the view that eosinophilic granuloma, Schüller-Christian's disease and Letterer-Siwe's disease in many respects must be regarded as different manifestations of the same basic disease-process (a virus disease?); but they claim that solitary, non-cranial eosinophilic granulomas need not necessarily be related to Schüller-Christian's disease. — An editorial in J. A. M. A. (April 47) supported this view. It was rather keenly opposed in a contribution by THANNHAUSER (50). He emphasized that the accuracy of the view set forth by FARBER and ENGELBRETH-HOLM and their coworkers cannot be questioned, and claimed that both he and MAGENDANTZ and several other authors have recognized the varying histologic picture in Schüller-Christian's disease. (FRASER and others, as mentioned above.) However, in a reply to this JAFFE & LICHTENSTEIN (31) insisted on their conviction that there was not in all cases any close relationship between the two diseases, and they emphasized that they had never seen any true transitional forms.

During the last 2—3 years several cases of eosinophilic granulomas of bone have been reported, in which various extraosseous localizations and such courses of the disease have been encountered that a close pathogenetic relationship with Schüller-Christian's disease must appear very plausible. As examples of these reports may be mentioned works by IMLER (29), ACKERMAN (3), WEINSTEIN, FRANCIS & SPROFKIN (53) all from the U. S. A., and GALATIUS-JENSEN (19) from Denmark. All the cases reported occurred in adults, and had a benignant course, but i

should, however, be noted that the observation periods have not been very long.

Also the relationship of Letterer-Siwe's disease with this group of diseases has been thoroughly examined during recent years. The Swedish investigators BESKOW (6) and BERG (5) both reported in 1946 definite transitions between Letterer-Siwe's disease and eosinophilic granuloma and Schüller-Christian's disease respectively. They both expressed the view that all three disease entities must be closely related. The Dutch investigator BARTELS (4) was of the same opinion. In 1947 he reported three cases of eosinophilic granuloma, one of which showed a definite successive development through all three groups.

The reason why this problem has been taken up for discussion here is that at the Radium Centre for Jutland and the Roentgen Department in the Municipal Hospital of Aarhus we have had an opportunity to see and study five cases from this group of diseases. All the five cases seem to give essential contributions to the understanding of the course and the interrelationship of these diseases, both clinically and patho-anatomically. The case histories, the results of the examinations, and the course of the disease in these five patients, who were all children, are reported in some detail.

Case I. (The Radium Centre for Jutland, Rec. No. 1286/47.) One-year-old girl. An only child. Birth and development natural. — Five months prior to admission here a well-defined, somewhat tender, and slowly growing »bump» in the left temporal region developed spontaneously. Otherwise no signs of disease. — Three months later fever and discharge from the left ear. On admission to an ear clinic the patient showed a tender, tense swelling in the left temple, discharge from the ear and a polypous tumour in the external auditory canal. There was fever (38—39° C) and a pronounced anemia (Hgb. 45 %). Roentgen examination of the skull revealed an approx. 2 × 3 cm large, sharply delimited defect in the left fronto-temporal region. — The polypous ear tumour was removed, and penicillin, iron and liver preparations were given. The fever persisted, the hemoglobin percentage rose to 60.

Microscopic Examination of the ear polypus and of tissue from the tumour revealed non-specific granulation tissue. — Judging from the clinical signs it was believed to be a malignant disease (sarcoma?), for which reason she was hospitalized here.

Clinical Examination: The patient was rather weak, anemic, emaciated, and febrile, and had a firm, somewhat tender swelling in the left temporal region and a similar, somewhat smaller swelling in the right temporal region. There were discharge and hemorrhage from both ears. The cervical lymph nodes were swollen; no definite swelling of the spleen, but slight enlargement of the liver. No skin symptoms, no exophthalmos, and no polyuria.

Roentgen Examination: The skull: Sharply delimited, 2 × 3.5 cm large defect in the left temporal region, a smaller defect in the right temporal bone, and two small lesions in the left parietal region. The thorax: Several cystic bone destructions in the costae, and several destructions in both scapulae. The lungs: Nothing abnormal. Other parts of the skeleton: Five larger, unilocular and multilocular cystic destructive processes in both femora and the pelvis. *Roentgen Diagnosis:* Scarcely bone sarcoma, probably a systemic disease, Schüller-Christian's disease?

Biopsy from the right femur: *Eosinophilic granuloma.*

Other Examinations: Hemoglobin: 53 %. Erythrocytes: 2.76 millions. Leukocytes: 10,400 with 62 % neutrophils, 3 % eosinophils, 1 % myelocytes, 16 % lymphocytes, 16 % monocytes, and 2 % plasma cells. Sternal aspiration: Normal bone marrow (Bichel). Blood cholesterol: Not examined. Tuberculin test: Negative. W. R.: Negative. Urine: Nothing abnormal. Normal diuresis. Treatment: 600 r to the right femur and 650 r to the left temporal region.[1] Iron preparations were given.

There was no response at all to the treatment. The course of the disease continued downhill; new foci developed, particularly in the skull, and those originally present grew. There were constant fever, a tendency to bleeding, and progressive anemia. The lymph nodes increased in size. At last a slight left-sided exophthalmos was noted. — The parents wanted to have the child removed to their home, and she died three months later after a total disease period of 8—9 months.

Microscopic Examination: 1) and 2) Tissue from the ear polypus and from the tumour from the left temporal region: Granulation tissue composed of young fibroblasts, vessels, and a very large number of reticular cells and young mesenchyma cells with infiltrations of leukocytes, plasma cells and lymphocytes; also some uncharacteristic necroses. Microscopic Diagnosis: *Non-specific granulation tissue* (Engelbreth-Holm) (Fig. 1).

3) Tumour-like tissue from the right femur: Finely fibrillated connective tissue with marked infiltration of eosinophilic and neutrophilic granulocytes and scattered giant cells of the myeloclast type. In some places of the periphery the cells were larger, bright, a little vacuolated, but not typically foamy. Microscopic Diagnosis: *Eosinophilic granuloma* (Tage Lund) (Fig. 2).

Case II. (The Radium Centre for Jutland, Rec. No. 2790/46.) A three-year-old girl. No. 6 of six children. Past history of excellent health. Two months prior to admission the child began to limp and complained of pain in the right femur, possibly after a preceding minor trauma. Swelling appeared in the distal part of the right femur, and as a roentgen examination seemed to suggest osteosarcoma, she was admitted to this department.

Clinical Examination revealed a well-nourished child of fairly good general condition. Owing to the pain she would not stand on the right leg; it lay outward rotated and semiflexed. Just proximal to the right knee there was a firm, circular, tender swelling, which increased the circumference of the right femur by 5 cm. Slight eczematous dermatitis in the face; no exophthalmos; no swelling of the spleen or liver, but a slight microadenitis. The diuresis was normal. Subfebrile temperature, 37.5—38° C.

Roentgen Examination: Right femur: The distal 5 cm of the metaphysis transformed into a multilocular, distended, cystic bone tumour. The cortex was very thin, possibly fractured. Some periosteal proliferation proximally, no spicule formation (Fig. 3). The skull: Five smaller, round, sharply delimited bone destructions in the theca cranii. Other parts of the skeleton: Cystic bone destruction in the left femur (Fig. 4), right radius, left ileum, and in several costae.

Roentgen Diagnosis: Osteitis fibrosa?? Myelomatosis? Hand-Schüller-Christian's disease?

Biopsy from the right femur showed: Xanthoma — Hand-Schüller-Christian's disease.

Other Examinations: Hemoglobin: 80 %. Erythrocytes: 4.30 millions. Leukocytes: 12,200 with 73 % neutrophils, 19 % lymphocytes, and 8 % monocytes. Slight anisocytosis.

[1] All roentgen dosages refer to air measurements. The factors of irradiation were 160 Kv, 4 Ma, 1 Cu + 1 Al, 40 cm, where no other definite statement is given.

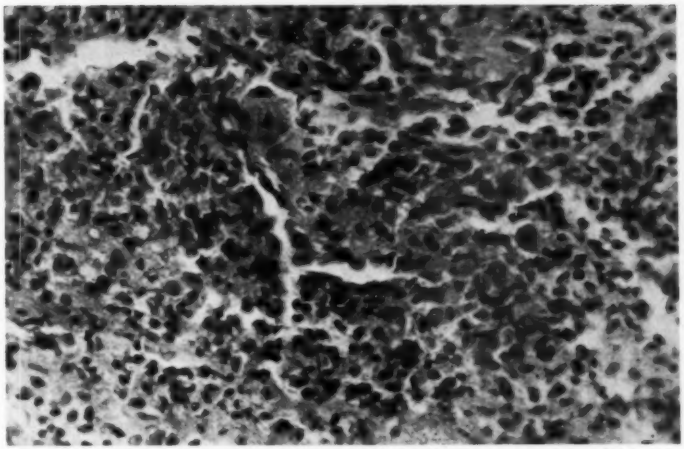

Fig. 1.

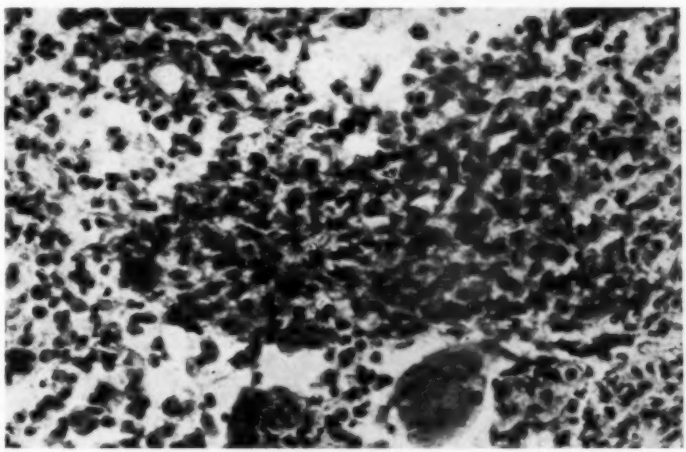

Fig. 2.

Sternal aspiration: No abnormal cell forms; the granulopoiesis slightly increased at the expense of the erythropoiesis (Bichel). — Serum calcium: 10 mg%. Serum phosphorus: 4.74 mg%. Acid serum phosphatases: 0.8 unit. G & G/100 ml (Holm-Jensen). The serum lipoid determination failed. Tuberculin test: Negative. W. R.: Negative. Urine: Nothing abnormal. Normal diuresis.

Treatment: 2,700 r to the right femur, 1,050 r to the left hip; three fields of the thorax

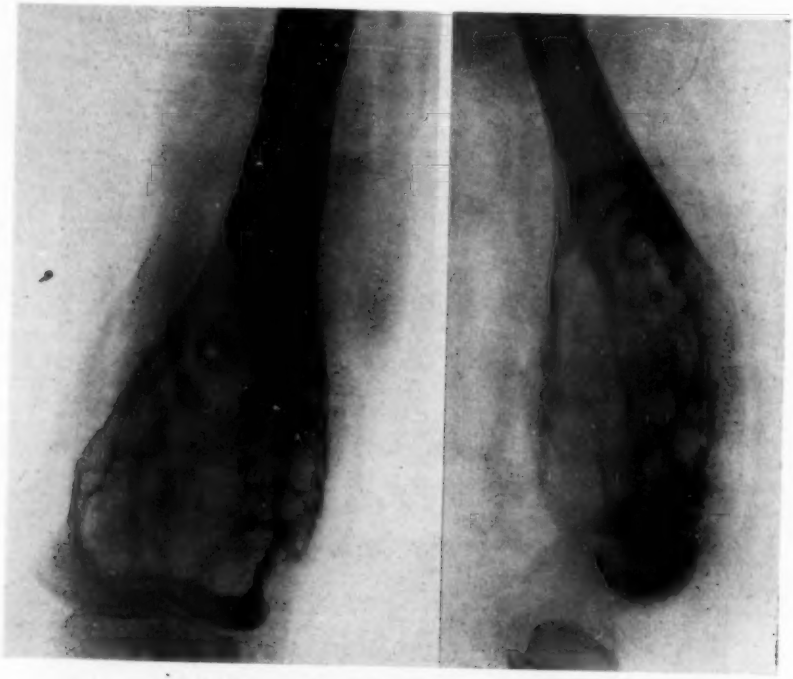

Fig. 3.

Fig. 4.

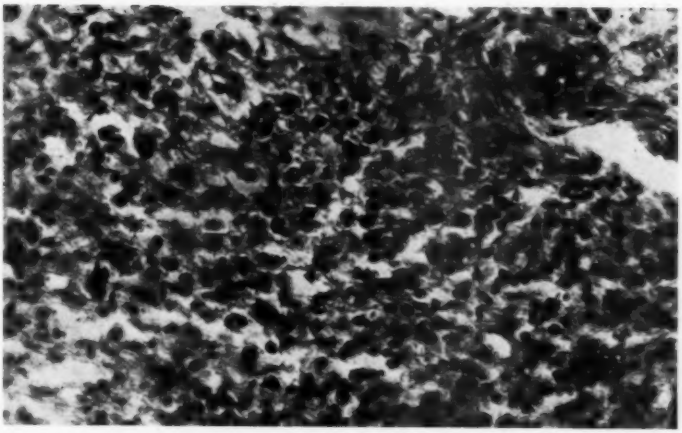

Fig. 5.

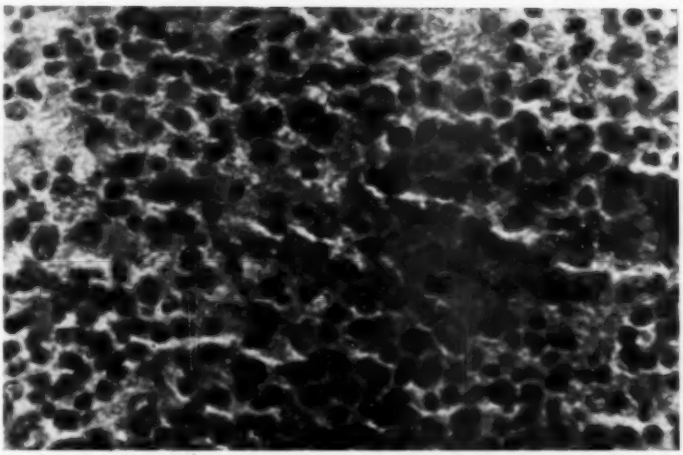

Fig. 6.

received 500 r each, and a dose of 600 r was directed to the parietal region. The right leg was splinted owing to a spontaneous fracture.

For the first 2—3 months, *i. e.* during the roentgen treatment and some time after, the condition remained fairly stationary, but then a rather quick downhill course commenced. The bone foci which had received treatment seemed for some time to show a certain tendency towards healing, but later a marked progression set in, and new foci developed, particularly in the skull. Also the anemia increased in severity, and a moderate exophthalmos developed. Three months later roentgen treatment was reinstituted,

a total of 1,950 r being given to four cranial fields, but no response was obtained. On the third and last admission the patient was very weak, emaciated, anemic (Hgb.: 41 %), anoretic, and dull. The bone defects showed a violent progression. There were fever and frequent vomiting. No increase of the diuresis. Moderate exophthalmos was still present. The patient succumbed three weeks after the admission after a total disease period of 3 months.

Autopsy: Xanthoma multipl. ossea. Hyperplasia lienis. Steatosis hepatis. Anemia m. g. organorum. Oedema pulm. Bronchitis.

Microscopic Examinations: 1) Tissue from the right femur: In some portions of the tissue a distinct infiltration of lymphocytes and eosinophilic leukocytes, and a great many large, bright, swollen cells with a foamy cytoplasm were found in a delicately fibrillated connective-tissue marrow. In other, more necrotic portions of the tissue a reticular basic tissue with numerous eosinophilic leukocytes and a few giant cells was seen.

Microscopic Diagnosis: *Xanthoma — Hand-Schüller-Christian's disease* (Tage Lund). (Fig. 5.)

2) Microscopic examination of autopsy specimens: Tissue from various bones: The picture varied from a very loose, almost liquescent tissue with very large, swollen »foam cells» to a fairly dense proliferating reticular tissue with infiltration of eosinophilic leukocytes, lymphocytes, and scattered giant cells of the myeloclast type. The reticular cells showed a tendency to develop into »foam cells». (Fig. 6.) — The spleen: The follicles were few and small, everywhere rather marked proliferation of the reticular cells, but no signs of lipoid accumulations. Scattered hematopoietic foci. — The liver: Marked fatty degeneration, but no proliferation of the reticular cells or connective tissue. Weak traces of hematopoiesis. — The kidneys, adrenal glands, and thyroid gland: Nothing abnormal.

Microscopic Diagnosis: *Hand-Schüller-Christian's disease* (Tage Lund).

Case III. (The Radium Centre for Jutland, Rec. No. 2887/47.) A boy, aged $3^1/_2$ years. Past history of good health. Following a rather severe trauma to the forehead a somewhat tender intumescence just over the right eye developed in the course of about six months. Otherwise, no signs of morbid conditions in the child. The tumour was 5×5 cm, and the roentgen examination revealed a corresponding defect in the right frontal bone. The tumour was diagnosed as a dermoid cyst; it was removed at the Neurosurgical Department of this hospital. Already at the operation it became obvious that it was not a dermoid tumour, and the microscopic examination revealed *reticulum cell sarcoma.*

After this diagnosis he was transferred to our department for roentgen treatment, the right frontal region receiving 800 r. He was considered a desolate case because some small areas of lessened density in the left scapula were interpreted as metastases. As the general condition was good, and no other anomalies were found, the child was discharged.

A few weeks later pain, discharge from the right ear, and fever developed. An otologic examination revealed a polypous tumour in the right external auditory canal. The tumour was removed, but no other therapy instituted. Microscopic examination showed sarcoma?, and the ear disease was interpreted as a manifestation of a metastatic process in the right temporal bone (no roentgen examination).

During the following period the patient's course continued downhill. The discharge from the right ear, and later also from the left, persisted. Four months after the first hospitalization the patient was readmitted for renewed roentgen therapy (January 1948).

Clinical Examination: The boy was rather weak, small for his age, and of slender build (height and weight unchanged from the first admission). Abundant discharge from both ears, which were filled with granulation masses. In the right cheek a firm in-

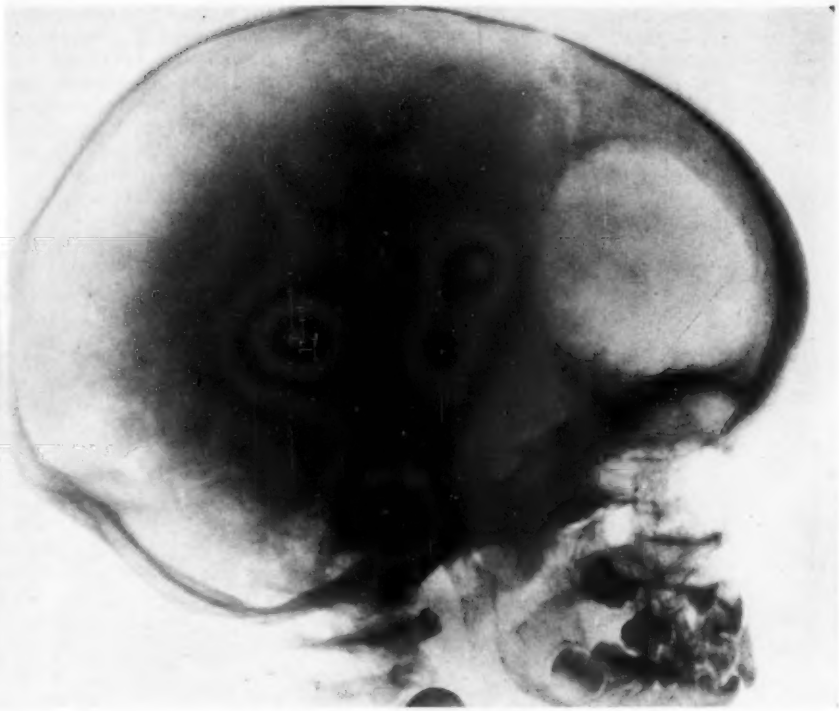

Fig. 7.

filtrate fixed to the mandible was elicited. No swelling of the liver or spleen; no peripheral adenitis; no exophthalmos, and no polyuria.

Roentgen Examination: The skull: The defect in the right frontal bone had increased in size, and a new lesion in the right parietal bone and an extensive destruction in the right side of the mandible were disclosed (Fig. 7). Left scapula: The small defects had fused into one large area. The rest of the skeleton: A new cystic destruction was found in the proximal part of the left radius, otherwise nothing abnormal.

Biopsy from the left radius: *Eosinophilic granuloma.* — Transition to Hand-Schüller-Christian's disease?

Other Examinations: Hemoglobin: 94 %. Erythrocytes: 4.91 millions. Leukocytes: 13,500 with 69 % neutrophils, 6 % eosinophils, 17 % lymphocytes, and 8 % monocytes. — Serum cholesterol: Total 131 mg%; free 39 mg%. Tuberculin test: Negative. Urine: Nothing abnormal; normal diuresis.

Treatment: 1,800 r to the right ear and cheek.

The general condition improved; the swelling of the right cheek, the granulations in the right ear, and the discharge subsided. However, this improvement proved to be of short duration.

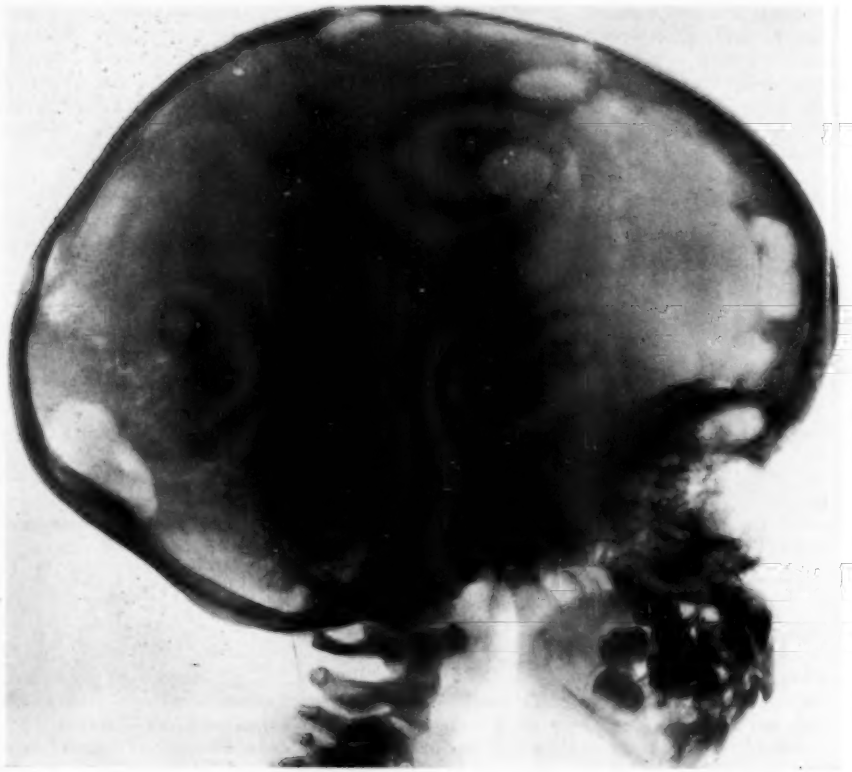

Fig. 8.

During the last year or so the disease has continued to aggravate. The boy has later been readmitted four times (March, June, and November '48, and March '49) for renewed roentgen therapy, which seems to have had a certain, if only transitory effect, and it cannot at all keep pace with the progression of the affection. All the time new bone lesions appear, and the old defects increase in size. The skull has now a typical maplike appearance (Fig. 8), the left scapula is completely destroyed, and the same applies to the entire right half of the mandible, and in almost all bones there are one or more foci (Fig. 9). Progressive anemia and recurring attacks of stomatitis and dermatitis persist. The last of these affections appears as a severe, exudative, eczematous dermatitis with large greasy crusts, especially in the scalp, the palms, and on the abdomen. Also the ear affection has recurred. Finally, a moderate, but progressive exophthalmos of the right eye has developed. The diuresis has been normal all the time. On the other hand, the growth has almost ceased. (From September '47 to March '48 the child has only grown from 86 to 87 cm. The weight has been fairly constant, about 12 kg, but has now decreased to 10 kg.)

The boy is now at home. The prognosis is very bad.

Microscopic Examinations: 1) Tissue from the fr ntal tumour: Very rich in cells and composed of l osely embedded, round and polygonal, or slightly s indle-shaped cells with deeply staining nuclei. The c ls showed radial arrangement around scattered, th n-walled vessels. Staining with silver showed a fi e mesh-work of reticular fibrils. Large areas of th tissue were necrotic and surrounded by infiltrati ns with eosinophilic leukocytes. — Microscopic D gnosis: *Reticulum cell sarcoma* (W. Munck).

2) Tissue from the ear polypus: Pre-eminently gr nulation tissue with widespread necroses and de se infiltration of lymphocytes and polynuclear le kocytes. Partly hidden by this, in some places a tumour-like tissue, rich in cells and composed of large, round cells, was seen. Microscopic Diagnosis: *Presumably sarcoma*, but owing to the necrosis and inflammation a closer classification was impossible (Tage Lund).

3) Tissue from the right radius: Tumour-like tissue, composed of a large number of reticulum-like cells. In some places the cells were fairly small, while in other places they were large, swollen, and with a bright cytoplasm, and finally, a few scattered typical »foam cells» were found. Besides, numerous streaks and clusters of eosinophilic cells were seen. Microscopic Diagnosis: *Eosinophilic granuloma with transition to xanthoma formation* (Tage Lund).

Fig. 9.

Case IV. (The Radium Centre for Jutland, Rec. No. 3362/45.) A boy, aged six; a twin. (The twin sister is alive and has never shown any signs of such affections or other anomalies.) The boy had had no children's diseases, except chickenpox. At the age of three he was operated for bilateral otitis media. At this operation some »peculiar» granulations were removed from both external auditory canals (no microscopic examination). An exudative, yellowish, crust-forming eczematous affection of both auditory canals around the ears persisted for a long time afterwards. Roentgen therapy was given here, following which the eczema disappeared (600 r to each ear — 115 Kv, 4 Ma, no filter, 30 cm). Owing to a complaint of anorexia and fatigue he was also given light treatment (Jan.—Febr. '45).

Six or seven months later pain in the left leg, a limp, and a slowly increasing swelling on the inner side of the proximal part of the left tibia developed without any known cause.

Roentgen Examination revealed a multilocular, cystic bone destruction of the size of about 2 × 3 cm. There was a slight periosteal reaction, but no spicule formation (Fig. 10). As it was supposed to be a case of *osteitis fibrosa*, osteotomy with curettage of the cavity was performed, and the cavity was filled with plaster (Surgical Department). Microscopic examination of the yellowish tissue removed at the operation showed: *Hand-Schüller-Christian's disease.* — A few days later a small cutaneous tumour on his back was removed, and microscopy of this also showed: *Xanthoma* — Schüller-Christian's disease?

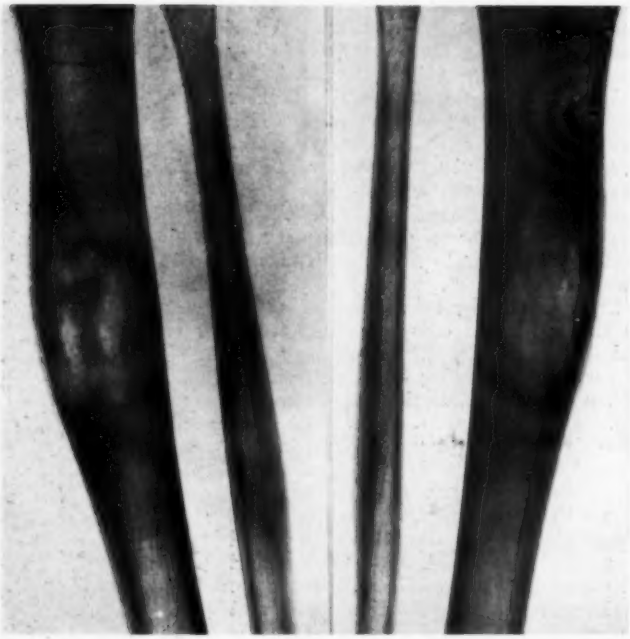

Fig. 10.

The child was then transferred to this department for roentgen treatment.

Clinical Examination: A slender boy of rather small stature; possibly with a slight bilateral exophthalmos. A moderate swelling of the proximal part of the left tibia and a firm, rather ill-defined thickening of the distal part of the left femur were found, but otherwise nothing abnormal. No tenderness or pain; normal temperature.

Roentgen Examination: Lower extremities: Plaster-filled cavity in the proximal part of the left tibia. In the distal part of the left femur a 3×2.5 cm large, cystic destruction of the same character was found. In the distal part of the right fibula there was a similar, but smaller lesion. The skull and the rest of the skeleton: Nothing abnormal.

Other Examinations: Hemoglobin: 85 %. Erythrocytes: 4.65 millions. Leukocytes: 10,400. Differential count: Nothing abnormal. Sternal aspiration: Normal bone marrow (Strunge). — Serum calcium: 8.4 mg%. Serum phosphorus: 6.2 mg%. Serum cholesterol: Total: 316 mg%, free: 103 mg%. — Tuberculin test: Negative. — Urine: Nothing abnormal. Diuresis and specific gravity normal.

Treatment: 1,500 r to the left tibia.

During the following two years the boy did not show any actual signs of disease, except that he did not increase in stature. His height remained unchanged from December '45 to April '48, 102 cm, and during the same period his weight was 15—16 kg. He had no complaints from his left leg. He had received two courses of light treatment owing to anorexia and fatigue, but without much effect. — The slight exophthalmos remained fairly unchanged. Roentgenograms taken at intervals showed that the defect in the left

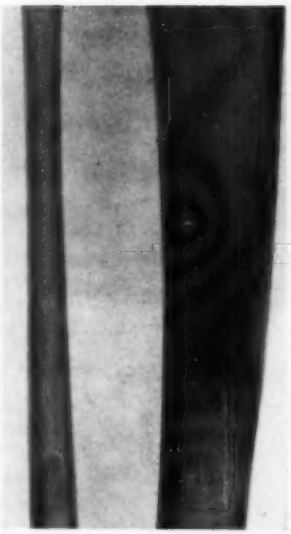

Fig. 11.

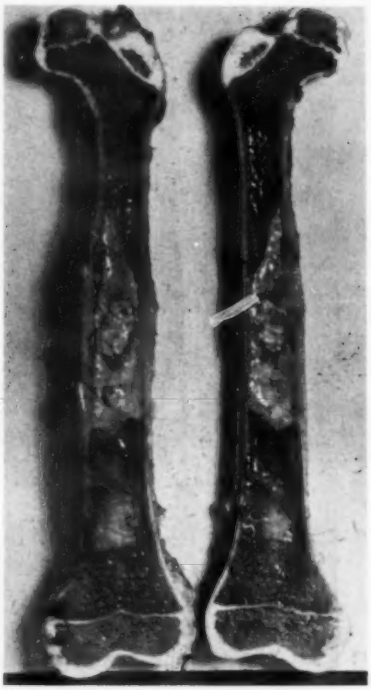

Fig 12.

tibia was healing slowly, the other lesions remained unchanged, and new destructions did not appear. — The hemoglobin percentage and the sedimentation rate were within normal limits.

In January '48 his condition aggravated rather suddenly. The complaints were thirst, polyuria, dizziness, headache, and nausea, and in the course of 2—3 months a progressive cerebellar ataxia accompanied by disturbances in the gait and intention tremor developed. Simultaneously the patient began to complain of pain in the left femur.

Clinical Examination: On the readmission the patient was very weak, debilitated, and apathic; there were definite ataxic symptoms, a distinct tremor, and pronounced bilateral nystagmus. The exophthalmos had slightly increased. Polyuria (approx. 2—3 litres daily). The appetite was very slight owing to frequent attacks of vomiting and nausea.

Roentgen Examination: Continued sclerotic healing of the process in the left tibia (Fig. 11), but marked increase in size of the cystic destructions in the right fibula, and especially in the left femur. Several new, smaller destructions in the skull were disclosed.

Otologic Examination: Normal hearing. — Pronounced bilateral nystagmus to both sides, yet most pronounced to the left. — Normal caloric reaction. Diagnosis: Vestibular affection (H. C. Andersen).

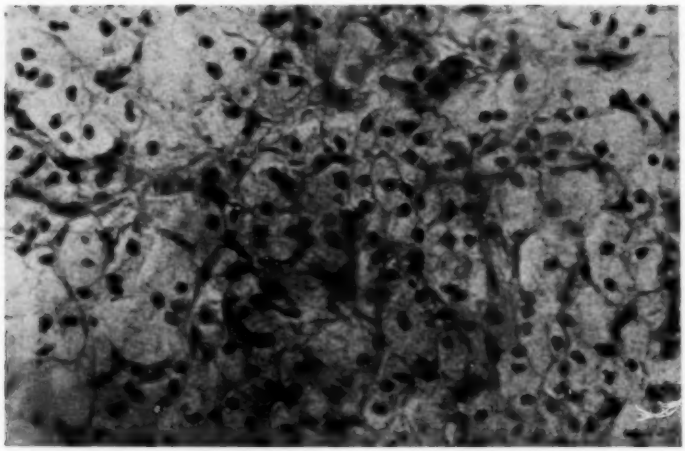

Fig. 13.

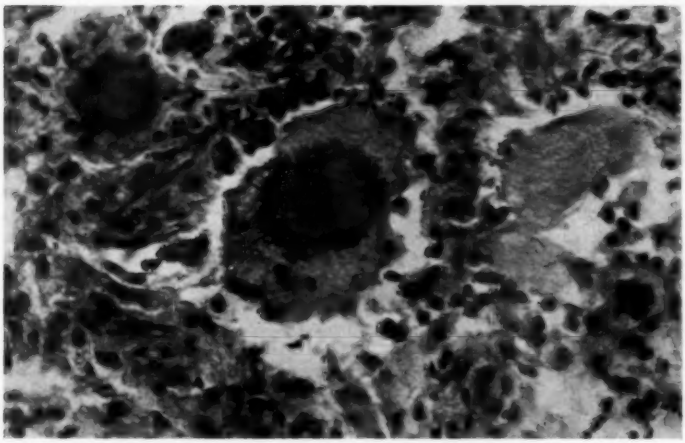

Fig. 14.

Ophthalmic Examination: Bilateral protrusion of the eyeballs. — Nystagmus. Ophthalmoscopy: Natural (V. Jensen).

Other Examinations: Hemoglobin: 105 %. Erythrocytes: 5.12 millions. Leukocytes: 8,400. Differential count: Nothing abnormal.

Roentgen therapy was instituted to the base of the skull and left femur, but had to be discontinued owing to the rapid progress of the disease. The cerebral affection increased in severity. The patient became delirious, had fever, and succumbed three weeks after the admission after a total disease period of three years.

Autopsy: Tumores xanthomatosi ossium variorum (Fig. 12). Xanthomata durae matris. Emaciatio — Bronchopneumoniae.

Microscopic Examinations: 1) Tissue from the left tibia. Loose connective tissue, partly composed of spindle-shaped, fibroblast-like cells, partly of polygonal cells, a great many of which were large and swollen with bright, foamy cytoplasm. Some scattered giant cells, which were on the whole very large and with foamy cytoplasm, were present (Figs. 13 and 14). There were also some infiltrations of lymphocytes and granulocytes, some of which were eosinophilic. Microscopic Diagnosis: *Hand-Schüller-Christian's disease* (W. Munck).

2) Tissue from the skin tumour: Principally the same histologic picture as in 1) (W. Munck). — All the »foam cells» stained deeply with sudan and had a constant granular appearance in both cases.

Microscopic Examination of the Autopsy Specimens: Various bones: Large clusters of bright cells with abundant granular foamy cytoplasm. In some places there were no cellular elements, but only precipitated crystals. — Dura: Inflammatory infiltration largely with esosinophilic cells. — The spleen: The follicles small; distinct proliferation of the reticular cells, which in many places were large, bright, and vacuolated. — The liver: Traces of fatty degeneration, but no change of the Kupffer cells. — The kidneys: The tubulus cells a little swollen, otherwise nothing abnormal. — The lungs: Scattered edema and inflammation. Microscopic Diagnosis: *Hand-Schüller-Christian's disease* — bronchopneumonias (W. Munck).

Case V. (The Radium Centre for Jutland, Rec. No. 2738/43.) (This patient is identical with Case 3 in the work published by Engelbreth-Holm, Teilum, and Erna Christensen.)

A boy, aged eight; No. 6 of six children; was well until the onset of the present disease. At the age of two years a slowly growing bump in the left side of the forehead appeared spontaneously. Except for the indolent tumour there were no other symptoms. A year later the tumour was removed (Neurosurgical Department). It had been expected to be a dermoid cyst, but at the operation a soft bone-marrow tumour was found in the frontal bone. Microscopic examination showed: *Eosinophilic granuloma.*

Roentgen Examination: The skull (prior to the operation): Cystic multilocular defect in the left frontal bone along the supraorbital margin, size $1^1/_2 \times 2$ cm. The entire skeleton: Nothing abnormal, except for the right ala ilii, in which there was a $3^1/_2 \times 2^1/_2$ cm large, multilocular defect, surrounded by several smaller lesions.

Clinical Examination: Nothing abnormal, apart from the tumour in the left frontal region and a moderate protrusion of the left eyeball.

Other Examinations: Hemoglobin: 85 %. Erythrocytes: 5.24 millions. Leukocytes 10,000. — Resting blood sugar: 112 mg%. — Serum cholesterol: Total: 200 mg%, free 59 mg%. — Urine: Nothing abnormal. Normal diuresis. — Tuberculin test: Negative. The patient was transferred to this department for postoperative *roentgen treatment* and was given 1,050 r to the left frontal region and 1,050 r to the right ileum.

During the following three years the patient reported at regular intervals for follow-up examinations. There were no complaints, but some inhibition of growth and mental retardation were apparent. Repeated roentgen examinations showed some sclerosis and decrease in size of the two bone defects, and no new foci appeared.

In the autumn of 1946 symptoms of a cerebral affection appeared, manifesting itself by an impediment in the speech, disturbances in the gait, and impairment of vision. The affection slowly developed into a severe cerebellar ataxia. At the same time the pituitary dysfunction increased in severity, causing the appearance of a pronounced

adiposogenital syndrome, while actual diabetes insipidus never developed, apart from a periodic, rather moderate polyuria.

During four periods of hospitalization in the course of the last two years (last time in December '48) courses of roentgen treatment, each of 1,200—1,500 r, were given to the posterior and medial cranial fossae. After each course there was a definite, but only transitory improvement. The disease progressed slowly, but surely. At the last hospitalization he was seriously disabled by the severe ataxia; he could neither stand, nor walk, and scarcely sit up. A pronounced intention tremor was present. His speech was slow, drawling, completely dysarthric. The mental retardation was very pronounced. Furthermore, there were signs of incipient bulbar paralysis, particularly affecting the glossopharyngeal nerve, and signs of lesion to the pyramidal tracts (bilateral positive Babinski). The vision of the left eye was markedly reduced, and moderate exophthalmos persisted. He was small of stature, but very obese, especially on the trunk and in the face, which had gradually assumed a typical »moon shape».

Roentgen Examination: The skull: No new foci, the defect in the left frontal bone almost healed. The skull relatively large, the sella turcica normal. — The pelvis: The defect in the left ileum almost healed. — No new foci were found in other parts of the skeleton.

Otologic Examination: Normal hearing. — Normal caloric reaction; no abnormal nystagmus (H. C. Andersen).

Ophthalmic Examination: Convergent strabismus of the left eye. Reduced vision of the left eye. Ophthalmoscopy: Nothing definitely abnormal (V. Jensen).

Other Examinations: Hemoglobin: 78 %. Urine: Nothing abnormal. The diuresis was rather large, but could not be measured as he wetted his bed.

Treatment: 2,100 r, distributed over three fields, to the posterior cranial fossa. — He improved slightly, became more lively, the tremor abated, but there was no essential change in the ataxia.

He is at home now. But it can scarcely be doubted that the disease will progress further, and especially the incipient bulbar paralysis is indicative of a poor prognosis, also quoad vitam.

Microscopic Examinations: Tissue from the left frontal bone: In some places a fairly homogeneous tissue, rich in cells and with diffuse proliferation of reticulo-endothelial cells, was seen. In other places the tissue was looser with newly formed vessels and distinct infiltration of leukocytes, particularly eosinophils, which in some areas lay in large clusters. Besides, there were also some histiocytes, which occasionally showed transition to giant cells (Touton cells). Definite xanthoma cells were not found. Microscopic Diagnosis: *Eosinophilic granuloma* (J. Engelbreth-Holm).

Discussion

The clinical symptoms, roentgenologic and laboratory examinations, the patho-anatomical findings, and the course of the disease in these five cases present both similarities and variations, which both supplement and overlap each other, and which are obviously conditioned on the stage of development of the disease and on the localization and extent of the pathologic processes, but not on any essential difference in nature. — Below I have tabulated the distribution of a number of the most important characteristics from the five case histories and at the same

Table 1

Case No.	Age at onset of disease	Duration of disease	Course of disease	Number of bone foci. (Rtg. ex.)	Pituitary Symptoms:		Cerebral Symptoms:	Cutaneous Symptoms:	Exophthalmos.	Microscopic Examinations:			Fatal
					Diab. insipidus.	Others				prim.	sec.	At autopsy	
1.	5 mos.	8—9 mos.	acute *L-S.*	numerous. *H-S-C.*	0	0	0	(+) (*L-S*)	+ *HSC.*	non-specific gran.	*E.G.*		+
2.	2 yrs.	8 mos.	acute *L-S.*	numerous. *H-S-C.*	0	0	0	0	+ *HSC.*	*H-S-C.*		*H-S-C.*	+
3.	2 yrs.	25 mos.	chronic *H-S-C.*	innumerable. *H-S-C.*	0	Inhibited growth *H-S-C.*	0	+ *L-S.*	+ *HSC.*	Reticulum cell-sarc.	*E.G.*		
4.	3 yrs.	3 yrs.	chronic *H-S-C.*	3/7—8 *E.G./ H-S-C.*	+ *HSC.*	Inhibited growth *H-S-C.*	+ *HSC.*	+? *L-S?*	+ *HSC.*	*H-S-C.*		*H-S-C.*	+
5.	2 yrs.	6 yrs.	chronic *E.G./ H-S-C.*	2 *E.G.*	(+) (*HSC*)	Adiposo-genital dystroph *H-S-C.*	+ *HSC.*	0	+ *HSC.*	*E.G.*			

time stated under which of the three groups the various symptoms must be classed.

Both the general impression and a review of the individual cases lend support to the opinion that the five cases reported here represent transitional and mixed forms of the three clinical pictures under discussion.

There were a large number of symptoms with many variations, but only the cutaneous and cerebral symptoms will be discussed here.

The cutaneous manifestations found especially in the third patient had the form of a greasy, exfoliative, eczematous, somewhat hypertrophic granulating dermatitis, which far into the course of the disease showed a tendency to recurrence. The localization was especially the scalp and the palms, but also the trunk. The affection closely corresponds to the types of dermatitis which have been described in Letterer-Siwe's disease. HAXTHAUSEN (24) and CURTZ (13) demonstrated similar skin symptoms in two children, aged 2 and $1^1/_2$ years, who both had bone lesions in the skull. In addition to this actual dermatitis this patient also had, as already mentioned, another epithelial manifestation, namely the »peculiar» polypous granulations in the external auditory canals. The patients No. 1 and No. 4 had similar polypous granulations in the ears. Only in one case (No. 3) the granulations were examined microscopically, but the result was rather obscure, perhaps suggesting sarcoma. These ear

affections have not been considered points of great importance, but it seems worthy of note that the description in all three cases has been quite uniform, and that the affection in all three cases has appeared in the initial stages of the disease. In my opinion it will be worth while to pay more attention to this phenomenon in future. By a review of the literature I have succeeded in finding observations of similar ear symptoms only in two cases, namely the third case reported by BARTELS (4) and the second case reported by AHLSTRÖM and WELIN (2). HAXTHAUSEN has seen a case of a similar polypous ear ezcema (personal communication).

As compared with the conditions in the relatively few cases previously reported the cerebral deficiency symptoms were very pronounced in the two cases described here, but of similar character. SCHÜLLER (43), CHESTER (9), CHIARI (10), and VAN BOGAERT (7) have each described one case, and VAN BOGAERT refers to another 2—3 cases. As in cases 4 and 5 reported here it was especially a question of an affection of the cerebellar tracts, accompanied by ataxia and tremor. In a few cases signs of bulbar paralysis and lesion to the pyramidal tracts have been encountered.

Of the laboratory examinations it is particularly the determinations of serum cholesterol which are of interest. For the two first patients no results are available. In the last three patients the amounts of total/free cholesterol in the serum were 131/39, 316/103, and 200/59 mg% respectively. KORNERUP (32) fixes the upper limit for normal total cholesterol at 300 to 320 mg%. The high values found for Case 4 is thus at the very limit. — It must be remembered that this patient also had some cutaneous xanthomas, which were presumably of a quite different origin, which may explain the hypercholesterolemia. — On the whole the hematologic examinations disclosed simple hypochromic anemias, which, however, in Cases 1 and 2 developed into severe aplastic anemias, which progressed parallel with the xanthomatous replacement of the bone marrow. The »white» blood picture was almost invariably characterized by a moderate neutrophilic leukocytosis, but no distinct eosinophilia.

The difficulties in making a differential diagnosis appear partly from the case histories, and partly from the introduction of this article, and will not be discussed further.

The principal treatment has in all five cases been roentgen irradiation, which has undoubtedly had a favourable effect both on the local manifestations and the general symptoms, but it has only been a question of remissions, often of a very short duration; no curative effect has been obtained. In one case (No. 4) surgical intervention seems to have resulted in healing of a bone focus, while in two cases (Nos. 3 and 5) no effect was obtained. In all three cases roentgen therapy was also applied.

The histologic examinations and with them also aspects of the etiology will be discussed in some detail.

Like the clinical findings, the histologic examinations showed gradual transitions and a certain continuous development of the disease, both in the individual case and in the five patients as a whole. The theories set forth both by WALLGREN and ENGELBRETH-HOLM, TEILUM, and ERNA CHRISTENSEN, that Letterer-Siwe's disease and the eosinophilic granulomas, respectively, must be regarded as different phases of Schüller-Christian's disease, are definitely confirmed, and it seems obvious that all three affections belong to the same disease entity. In the system of phases introduced by ENGELBRETH-HOLM and coworkers, the cases of Letterer-Siwe's disease indubitably represent the first hyperplastic, reticulo-histiocytic phase. The next two, the granulomatous and xanthomatous phases, correspond to the eosinophilic granulomas and Schüller-Christian's disease. The fourth phase, characterized by fibrous healing processes, comprises the chronic cases, and the large number of eosinophilic granulomas, which according to the reports have undoubtedly had a benignant course, may, perhaps, be classed under this group. There is no reason to believe that any one case of the disease should necessarily pass through all four phases. If a case with one or a few eosinophilic granulomas of bone rapidly develops into the fourth phase, it will result in a benignant course, and deficiency symptoms cannot be expected in such a case. Depending on the degree of generalization, other cases may very well show considerable deficiency symptoms in the fourth phase. As already mentioned, this holds good of most chronic cases of Schüller-Christian's disease.

Of the five cases reported here Nos. 1, 3, and 2 show a continuous development through the first three phases, the first, second, and third phase, respectively being most distinct. In Case 4 a definite third phase, with pronounced xanthoma formations, is seen. Case 5 must represent a borderline case between the third and fourth phases, since both healing of the bone destructions and progression of the cerebral and pituitary processes were found.

The factors determining this phaseal development and the varying tendency to generalization are quite unknown. The age, at which the disease occurs or manifests itself, plays a certain part. The variation of the course ranges from acute in infants, corresponding to the Letterer-Siwe phase, to a more protracted, generally malignant course in older children, whether the disease has been recognized in the first, second or third phase, and named correspondingly. In young individuals and adults a chronic course, most frequently of benignant character, is generally encountered. This holds good especially of the eosinophilic granulomas, but also sometimes of cases of Schüller-Christian's disease. From Norway

MELLBYE (38) has recently reported two chronic cases in adults. Particularly one of them had a very protracted and benignant course (20 years). (In my opinion it may perhaps be interpreted as a case in the fourth phase with very few symptoms.)

On the basis of these considerations, the combinations found in the five cases reported here, and a review of the literature it may be concluded that Schüller-Christian's disease, Letterer-Siwe's disease, and the eosinophilic granulomas must be regarded as different appearances, dependent on the phase, of the same disease, and that it is a disorder of the reticulo-endothelial system.

The understanding of the pathogenesis of the disease group is not widened by its classification under the reticuloses. Nothing is known as to what conditions this abnormal development of the reticulo-endothelial cells, nor the reason why these peculiar granulomatous and xanthomatous formations occur in this disease group. It is not even possible to decide with any certainty if it is a question of neoplastic or inflammatory processes. Our definitions of inflammation and neoplasia may not be sufficiently concise for these cases (v. D. MEER and ZELDENRUST (37)). In his latest work THANNHAUSER (51) expresses the opinion that the xanthomatous formations are due to an enzymic disturbance, particularly in young proliferating reticular cells, and he still claims the existence of a certain connection with Gaucher's and Niemann-Pick's diseases. It is possible that these diseases, and perhaps Tay-Sachs's disease, should also be grouped under the reticuloses.

It is of minor importance whether a collective term for this group of diseases is coined, or that the ordinary designations of the three phases are preserved, as used here. Clinically it seems practical to use the latter established designations. On the other hand, it is very important to realize that the three clinical pictures represent three phases of the same disease with an often very serious prognosis, and that the benignant phases may develop into a malignant disorder, especially in younger individuals.

Acknowledgement is gratefully made of the advice and assistance of J. Bichel, M. D. (The Research Laboratories of the Radium Centre of Jutland, Aarhus) and of the assistance of Tage Lund, M. D. (Patho-anatomical Institute, University of Aarhus) in the pathological studies.

SUMMARY

Five cases are reported and discussed. In each of them the disease is suggested to be a transitional form between Schüller-Christian's disease, Letterer-Siwe's disease and the Eosinophilic Granulomas of bone. In some of these patients there was evidence of all three conditions during the course of the disease. On the basis of this observation the author arrives at the conclusion that it is not a question of three differen

types of disease but rather of different phases of one and the same disease, constituting a disturbance of the reticulo-endothelial system.

ZUSAMMENFASSUNG

Fünf Krankheitsfälle werden wiedergegeben und besprochen, die alle als Übergangsfälle zwischen der Schüller-Christian'schen Krankheit, der Letterer-Siwe'schen Krankheit und den eosinofilen Knochengranulomen anzusehen sind. Bei mehreren der Patienten wird gezeigt, dass die Entwicklung alle drei Krankheitsbilder durchläuft. Hieraus folgt der Schluss, dass es sich nicht um drei verschiedene Krankheitsgruppen handeln kann, sondern nur um Phasen ein und desselben Leidens, das als eine Systemerkrankung des retikuloendothelialen Systems anzusehen ist.

RÉSUMÉ

Le travail relate et discute 5 cas pathologiques qui tous doivent être appelés des formes de passage entre la maladie de Schüller-Christian, celle de Letterer-Siwe et les granulomes éosinophiles osseux. Chez plusieurs des malades on démontre que l'évolution reproduit successivement tous les trois tableaux cliniques. Il faut en conclure qu'il ne peut pas s'agir de trois groupes de maladies différentes mais de stades de la même affection qu'il faut considérer comme la maladie d'un système, à savoir, du système réticulo-endothélial.

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ROENTGENOGRAPHIC STUDIES OF HYDRONEPHROSIS DUE TO OBSTRUCTION AT THE URETERO-PELVIC JUNCTION[1]

by

K. Lindblom

The main purpose of this paper is to elucidate the diagnostic possibilities of intravenous urography in contradistinction to retrograde pyelography in the study of hydronephrosis due to anomalous structures causing obstruction at the uretero-pelvic junction.

The premises are that retrograde pyelography is contraindicated in hydronephrosis because of a great risk of infection and that surgical therapy depends to a certain degree upon the roentgenographic information on the function of the kidney and the type of obstruction.

These informations are obtainable by a *prolonged urography*. The patient is lying on the back until the whole pelvis is filled with contrast medium. Repeated intravenous injections of the contrast medium are required and papaverin is usually also given. As soon as the pelvis is filled a compression apparatus is placed over the ureter in question and the observation continues until the ureter is filled. Then, with the compression over the ureter the patient is turned into such a position that the ureteropelvic junction can be studied. Finally, the same region is also roentgenographed after removal of the ureteric compression.

Pathogenesis and Course

The anomalous structures causing obstructions at the uretero-pelvic junction are:

1. Adventitial adhesions between the ureter and the pelvic wall.
2. Stricture or valve in the ureteric orifice.
3. Aberrant renal vessel crossing the ureter.

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In the present material the causes of obstruction are grouped as follows:

Operated cases	
Fixation	32 cases
» + Stenosis	16 »
» + Aberrant vessel	18 »
Stenosis	8 »
Aberrant vessel	6 »
Doubtful cause	3 »
Non-operated cases	
Fixation (Roentgen)	17 »
	100 cases

Fixation of the ureter to the pelvic wall by adhesions is the most common cause. These adhesions were demonstrated already in 1871 by SIMON and they have been the subject of several studies, of which the most exhaustive one was made by ÖSTLING in 1942. In most cases of stenosis, of valve within the ureteric orifice, and of aberrant vessel, there is also a fixation of the ureter to the pelvic wall. To analyse which hindrance is the most important one, may be difficult even at operation. HELLSTRÖM worked out an excellent method for the differential diagnosis by distending the pelvis through injection during operation.

The obstructions described above are looked upon as congenital in origin though, as a rule, they become manifest later on. The hindrance is not complete. An increased diuresis or a nephroptosis (Fig. 1) seem to be additional factors which make the outflow inadequate. As the pelvis distends the adventitial adhesions become streched and strangulate the ureter (Fig. 2 a—b). The distension of the pelvis rotates the renal hilus anteriorly thus streching an anterior aberrant vessel which compresses the ureter against the pelvis (Fig. 2 c—d). If a valve is present, an increased pressure in the pelvis will close the valve.

The distension of the pelvis may begin early in life and immediately become chronic; in these cases the kidney shows no function. In most cases the process starts in adults and the obstruction becomes intermittent; the patient has recurrent attacks of pains during which the pelvis is highly distended and the function of the kidney is bad, while in the intervals there is only slight or no distension at all and the function is good (Fig. 3—4). After a few attacks the obstruction may become permanent and the kidney destroyed (Fig. 5). In a large number of cases, a moderate hydronephrosis develops and remains constant without marked symptoms.

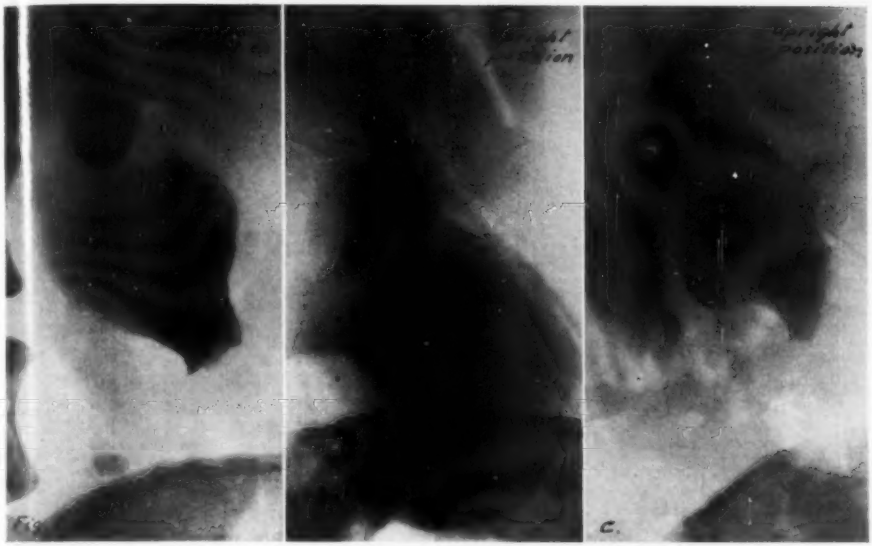


Fig. 1 a—c. Hydronephrosis aggravated by nephroptosis in upright position (*b*). Symptomfree after loosening of adventitial adhesions and nephropexy (*c*).

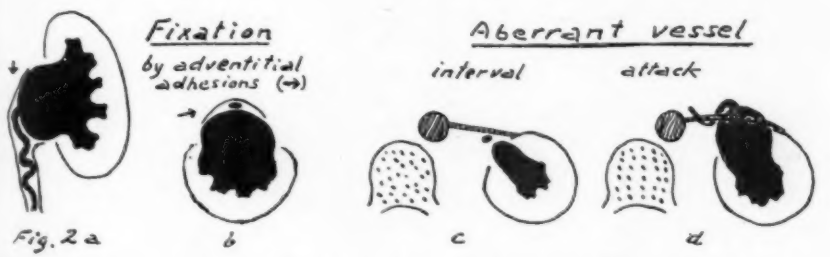


Fig. 2 a—d. Sketches demonstrating the mechanism of adventitial adhesions and aberrant renal vessels. In *b—d* the kidney is seen axially.

Roentgenography of the Hydronephrosis

Intermittent hydronephrosis, during attack. Excretion from the kidney is, as a rule, demonstrable on the films. Often there is just enough dye to fill a few calices only which show that the thickness of the parenchyma is little reduced; the kidney is more distended than destroyed. If the

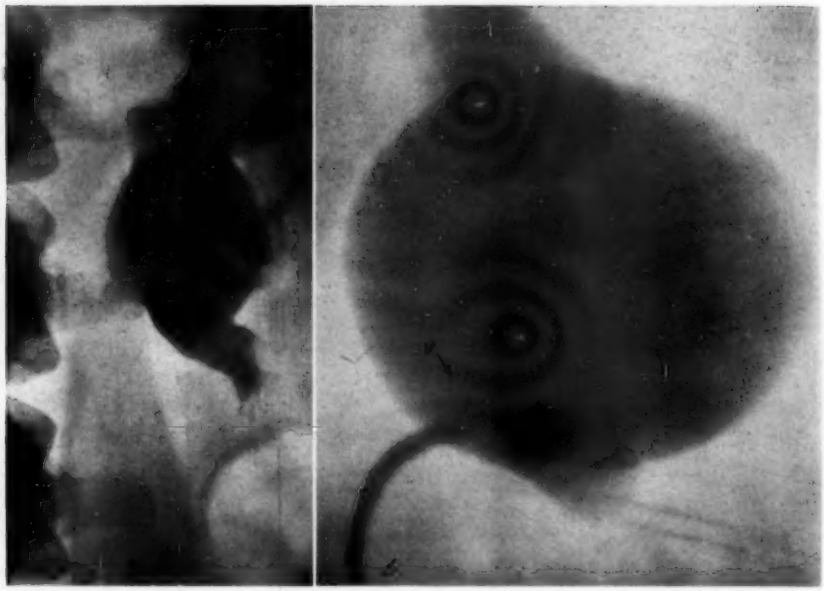
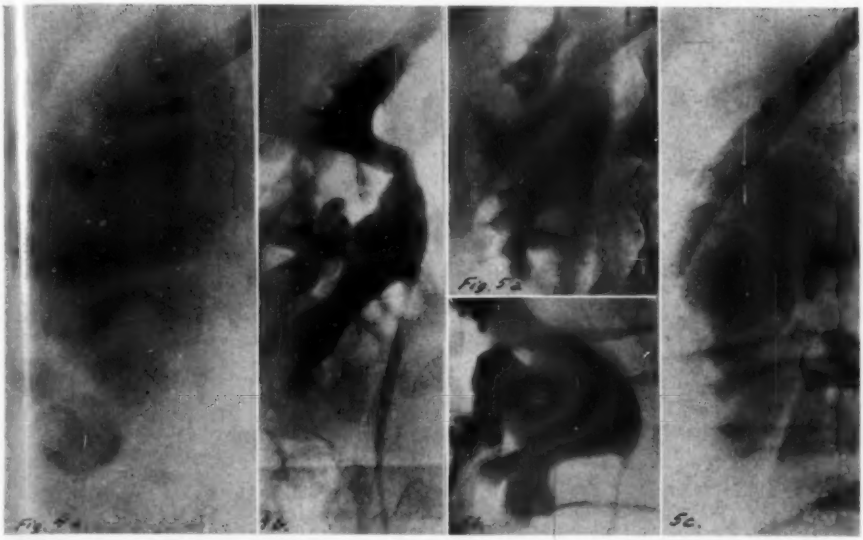


Fig. 3 a—b. Hydronephrosis by aberrant renal vessel. In *a* symptomfree interval; in *b* two days later during attack produced by the procedure of retrograde pyelography. Arrow marks the vascular pressure defect (*v*).

function is good, a diagnosis of obstruction is made. If no excretion is seen, even at prolonged urography the distended pelvis is usually visible as a bulging structure forming an anterior and medial continuation of the kidney. Surgical intervention is indicated without requiring retrograde pyelography.

Intermittent hydronephrosis, symptomfree interval. The kidney and the pelvis may appear quite normal. Often a straight contour of the pelvis against the psoas tells of a previous dilatation (Fig. 5). At this stage the procedure of a retrograde pyelography may provoke an acute dilatation (Fig. 3), but because of the risk of an infection, it is more reasonable to wait for the next spontaneous attack if the symptoms are not obvious enough to warrant an immediate operation. By distending the pelvis during operation, the differentiation is made between adhesions and aberrant vessel. In many cases, however, a moderate dilatation of the pelvis persists in the intervals and the diagnosis of the hydronephrosis and its cause can be made by prolonged urography.



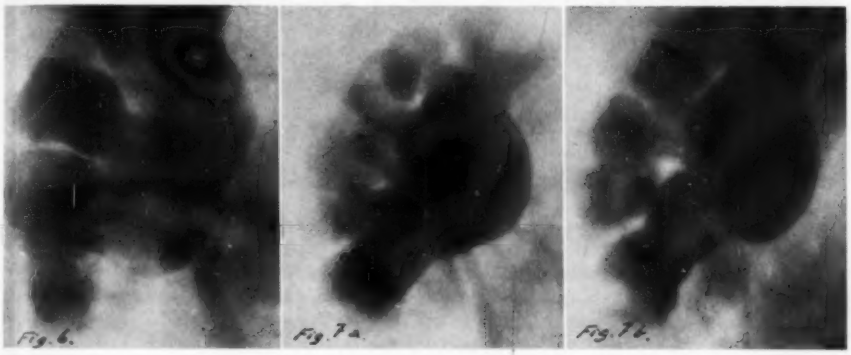
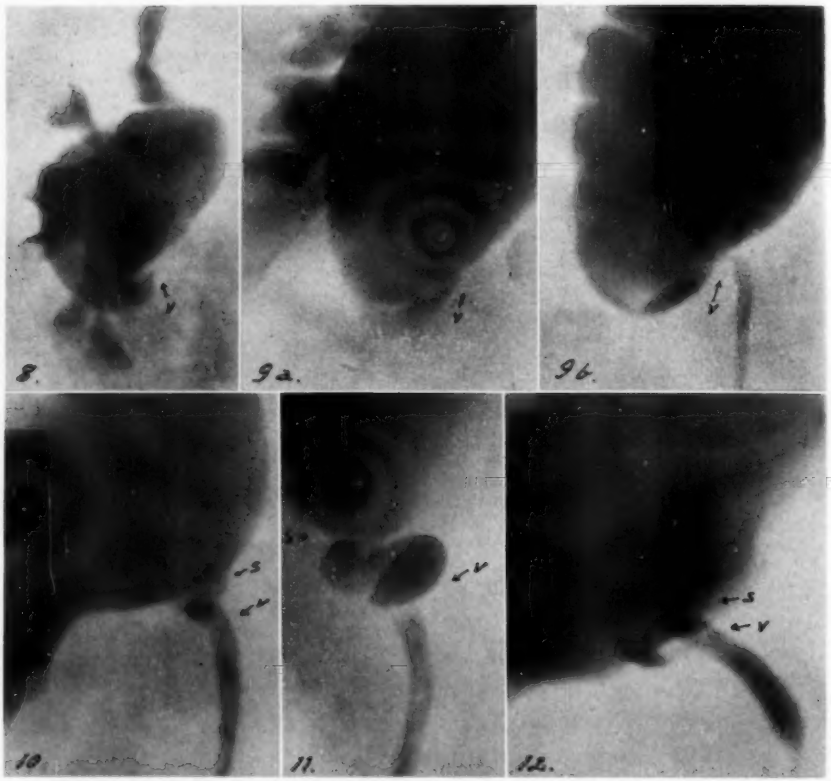


Fig. 4 a—b. Hydronephrosis by adventitial adhesions and aberrant vessel. In *a* during attack; in *b* after loosening of the adhesions and transposition of the vessel.

Fig. 5 a—c. Hydronephrosis by adventitial adhesions. In *a* and *b* probably during symptomfree interval; in *c* $1^1/_2$ years later, with highly aggravated hydronephrosis. Nephrectomy.

Figs. 6—7. Two cases of hydronephrosis by adventitial adhesions. The ureteropelvic junction is visualized by prolonged urography.



Figs. 8—12. Cases of hydronephrosis by aberrant renal vessels. In 8 and 9 an intravenous urography demonstrating the filling of the ureter proximal to the aberrant vessel. In 9 *b*—12 retrograde pyelography showing vascular pressure defects (*v*). At *s* the space between ureter and pelvis representing the thickness of their walls.

Permanent hydronephrosis, moderate stage. The function of the kidney is good and prolonged urography shows the hydronephrosis and its cause. Follow-up examinations of these cases usually show unprogressive hydronephrosis. The usual cause is adventitial adhesions.

Permanent hydronephrosis, late stage. This group is formed by the cases of total hydronephrosis without kidney function. The kidney and its pelvis form a huge sac. Retrograde pyelography is often required for diagnosis. No matter whether infection occurs or not, it does not influence the operative result because only nephrectomy can be made.

Differential Diagnosis of the Obstruction

Fixation of the ureter to the pelvis by adventitial adhesions. The ureter starts from the medial or anterior wall of the pelvis and runs along the pelvis in caudal direction (Figs. 6—7). The lower pole of the pelvis is often in caudal direction (Figs. 6—7). The lower pole of the pelvis is often elongated, that is, the pelvis is pear-shaped.

Aberrant renal vessel crossing the ureter. In these cases the ureter usually starts at the lower pole of the pelvis and runs medially where it rides on the vessel forming a knee before it continues in a caudal direction (Figs. 8—12). The vascular pressure defect of the ureter is demonstrable only if the rays are parallel to the vessel, that is, if the ureteric knee is seen in profile. In other projections the knee is seen shortened with a straight upper contour; about two millimeters above a parallel contour, belonging to the pelvis may be seen (Figs. 10—12). The space between these contours corresponds to the thickness of the ureteric and pelvic walls, it does not represent the vessel. When the ureter empties, the filling remains proximal to the knee, which is an important sign in the intravenous urography (Figs. 8 and 9 a). The distended pelvis is round.

Stenosis or valve formation need no special illustration.

SUMMARY

Improved intravenous urography, called prolonged urography, may to a great extent replace the dangerous retrograde pyelography in the study of hydronephrosis due to obstruction at the uretero-pelvic junction.

The roentgenography of the hydronephrosis in its different forms and stages and the differential diagnosis of this type of obstruction are described and illustrated.

ZUSAMMENFASSUNG

Verbesserte intravenöse Urographie, sog. verlängerte Urographie, kann beim Studium einer Hydronephrose durch ein Hindernis am Abgang des Ureters aus dem Nierenbecken die gefärliche retrograde Pyelographie in grossem Ausmasse ersetzen.

Das röntgenographische Studium der Hydronephrose in ihren verschiedenen Formen und Stadien sowie die Differentialdiagnose der Art des Hindernisses werden beschrieben und veranschaulicht.

RÉSUMÉ

Une urographie intraveineuse perfectionnée, appelée »urographie prolongée», peut remplacer dans une large mesure la pyélographie rétrograde avec ses risques, quand il s'agit d'étudier les hydronéphroses dues à un obstacle situé à la jonction du bassinet et de l'uretère.

L'auteur décrit et illustre l'étude radiologique de l'hydronéphrose sous ses différentes formes et à ses divers stades, et traite du diagnostic différentiel de la nature de l'obstacle.

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ELECTROKYMOGRAPHIC RECORDING OF AURICULAR MOVEMENTS[1]

by

Ture Andersson

In kymographic, electrokymographic or kinematographic examinations of the heart it is conspicuous that the areas where the auricles are border forming exhibit movements of rather changing appearance even in normal cases. As a result, varied conceptions of the nature of the auricular movements have been presented in the literature. This is perhaps especially true of the auricular appendages.

In electrokymography we have obtained a new means of recording the movements of the heart. The principle of electrokymography, its technical procedure and its sources of error will not be handled in this connection. In order to facilitate the interpretation of the curve and to determine the timing, a known curve is taken synchronously with the electrokymogram for comparison. We have previously used EKG but have changed to simultaneous recording of EKG and carotid sphygmogram.

The auricular electrokymogram from healthy hearts most often appears in the following way (Fig. 1). (On the curves which are reproduced the rising curve line depicts lateral movement and the falling curve line represents medial movement in the heart contour.)

During the ventricular systole there is a large positive wave with the maximum at the time of the opening of the auriculoventricular valves. This rising part of the curve is dependent upon the auricles being filled with blood and dilated during the ventricular systole.

After the auriculoventricular valves have been opened the auricles empty themselves into the ventricles and the curve falls more or less steeply during a time which corresponds to »rapid filling phase».

[1] Read at the Meeting of the Northern Association for Medical Radiology, June 10—12, 1949; submitted for publication June 30, 1949.

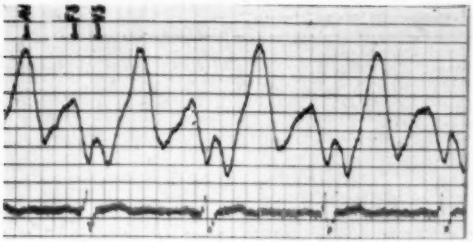

Fig. 1. Curve from the left auricle. AV = opening of the auriculoventricular valves. FS = beginning of the auricular systole. VS = beginning of the expelling phase.

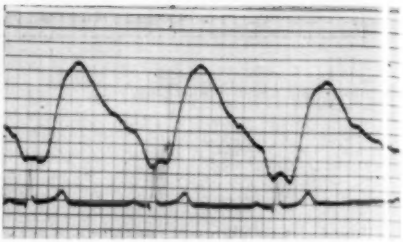

Fig. 2. Curve from the right auricle. The positive wave during the ventricular diastole is missing. Compare figure 1.

After this early diastolic emptying the curve rises again but in a lesser degree, depending upon the fact that the diastolic dilatation of the ventricles causes the auricular contour to displace itself outwards. Especially the vigorous movement of the atrioventricular septum against the base of the heart during the diastole would seem to be important in this connection. A slight increase of the auricular volume may also take place during this period.

The active emptying of the auricles is often marked by a steeply falling curve in connection with the P wave of the electrocardiogram. Later, as already described, during the ventricular systole including the phase of isometric contraction comes the large positive filling wave which, at the beginning of the ventricular expelling phase, is most often interrupted by a short negative wave. This is caused by the ventricular systole and perhaps most by the movement of the atrioventricular septum against the apex.

This auricular electrokymogram consists, accordingly, of both auricular and ventricular components, even though the former predominate. In certain cases, however, one of these ventricular components is missing, most frequently the diastolic (Fig. 2). In other cases both may be absent on the kymogram.

On the other hand, sometimes the ventricular components may dominate (Fig. 3). On the whole, it is true that the ventricular influence is greatest in the parts of the auricular contour which lie nearest the ventricle. Therefore, for example, the ventricular influence is greater in the caudal parts of the right heart contour than in the cranial.

Movements of the auricular contour are also entirely different if the patient is examined in horizontal position, as we most often do, or in upright position. In the latter case the ventricular components are

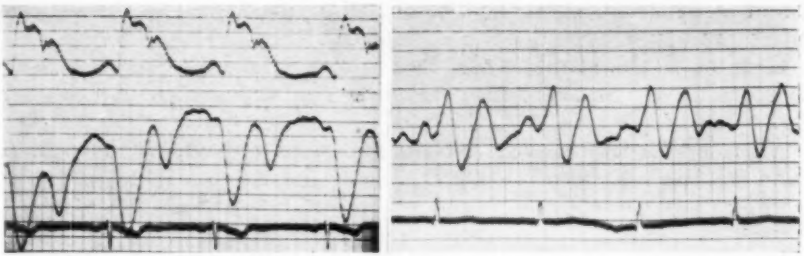

Fig. 3. Auricular curves in which the influence of the ventricles is great. (The upper curve in the left picture is a carotid pressure curve.)

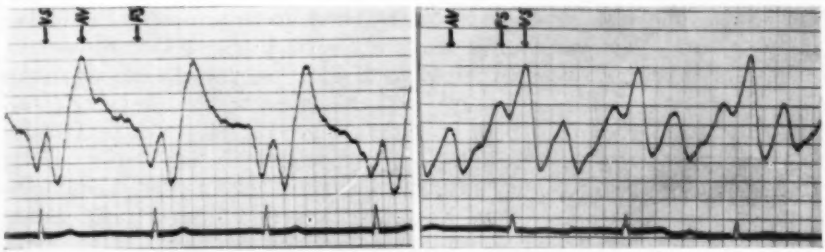

Fig. 4. Electrokymograms from the right auricle of the same patient at examination in horizontal (left) and upright (right) positions. In the latter case the ventricular components are more dominating. (Alphabetical designations as in figure 1.)

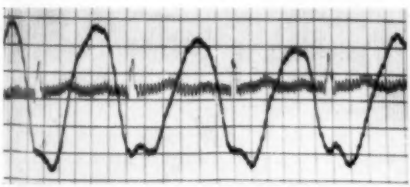

Fig. 5. Auricular curve in the case of tachycardia.

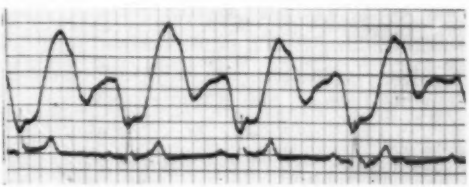

Fig. 6. Auricular electrokymogram. On the large positive filling wave there is a smaller superimposed wave corresponding to the isometric relaxation phase. (Refer to the text.)

more dominating, while the auricular filling and emptying wave becomes less prominent (Fig. 4).

The circumstances are the same if the curve is taken during deep inspiration, while the ventricular influence becomes less on expiration.

A further variation of the auricular kymogram is often seen in the

case of tachycardia, when the diastolic emptying wave and the auricular systole are superimposed upon each other. (Fig. 5.)

Changes in the shape of the heart during the isometric phases and the rotation of the heart also influence the appearance of the curve (Fig. 6).

All this makes auricular electrokymograms appear, at first glance, completely and essentially different.

The Region of the Auricular Appendage

The statements in the literature about the movements of the auricular appendages are not entirely in agreement. With radiokymography STUMPF found identical movements over the left auricular appendage and the right auricle with three waves corresponding to auricular filling and emptying, auricular systole and also transmitted ventricular movement. With radiokymography others found double waves, the one corresponding to the ventricular filling and emptying, the other to the auricular (DELHERM, FETZER). KÖTTGEN mentions that transmitted movements from the pulmonary artery and left ventricle dominate in the region of the left auricular appendage. Finally, according to FABRICIUS, the movements there are varied and uncharacteristic. He finds constant movements only during auricular systole and at the change between rapid and slow diastolic filling.

With electrokymographic examinations, often on the small area of the left heart contour between the left ventricle and the pulmonary artery, which is the site of the left auricular appendage, curves are obtained which are identical with those obtained over the right and posterior cranial contours, and accordingly, the regions where the auricles are border forming. This has previously been mentioned in the literature by LUISADA and the author.

The contour of the auricular appendage may be defined in certain cases by fluoroscopy or radiography between the ventricular and arterial arches. This is often impossible, however, notwithstanding that the electrokymogram from the area in question indicates that the auricular appendage is border forming through giving typical auricular movements.

In order to have a more certain understanding of the conditions we have specially penetrated the region of the left auricular appendage with frequent electrokymograms in 50 electrokymographic examinations. On account of its site, the right auricular appendage is not so suitable for an examination of this sort. The majority of the examinations have been made in connection with routine examinations of heart and lungs, and the majority of the patients have had healthy hearts. Some have had subjective difficulty. A few have had compensated mitral defects; a few

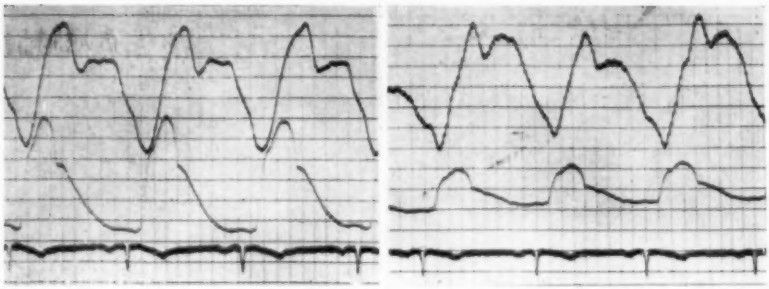

Fig. 7. Electrokymograms from the left auricular appendage (left) and the right auricle (right) in the same patient. The curves have the same appearance and relations to EKG and carotid sphygmogram.

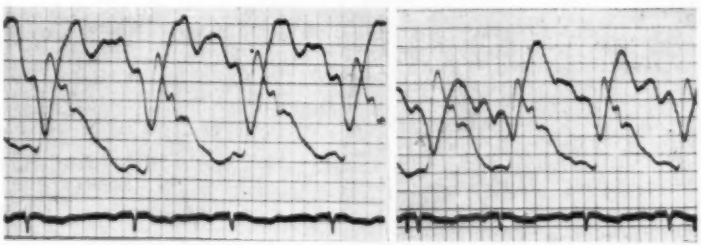

Fig. 8. Left auricular appendage (left) and right auricle (right) in the same patient. Identical curves. (EKG and carotid sphygmogram.)

have had light hypertension or thyreotoxicosis. All the examinations have been made in frontal projection.

In 45 cases auricular movements of the same appearance as on the posterior and right heart contours were obtained within a larger or smaller area between the left ventricular contour and the arch of the pulmonary artery (Fig. 7, 8, 9). On the whole, here, as in the caudal parts of the right auricular contour, the ventricular components are relatively prominent in the kymogram. Remarkably often, however, curves were obtained within a limited part of the area with completely dominating auricular components. Of course, caudally close to the ventricle or cranially close to the pulmonary artery transmitted movements will be more dominating. In most of these patients the arch of the left auricular appendage could not be distinguished on an ordinary frontal radiogram (Fig. 10).

In 5 cases, despite particular penetration of the area, no typical auricular movements were obtained, but instead a combination of ven-

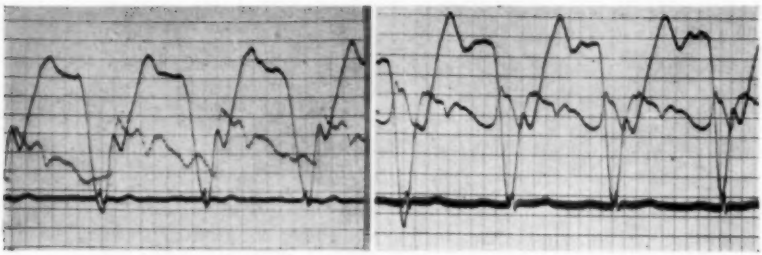

Fig. 9. Typical electrokymograms from the left auricular appendage in cases of mitral disease. The diastolic emptying is small, but there is a very strong auriculosystolic wave. (EKG and carotid sphygmogram.)

Fig. 10 a.

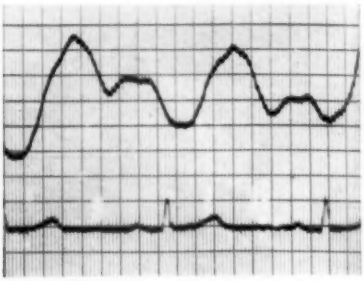

Fig. 10 b.

Fig. 10. Frontal picture of the heart in which no left auricular appendage contour can be distinguished. The electrokymogram (right) from the region of the left auricular appendage shows typical auricular movements.

triculo- and arterio-kymograms, and in addition, a negative wave corresponding to the auricular systole. Such a transmitted wave, however, is often found also on the arteriokymogram.

Probably the movements from an auricular appendage, which is contour forming in a very limited area between the ventricle and the pulmonary artery, can be drowned in their transmitted pulsations. Also the large branches of the pulmonary artery which are projected over this area must be taken into consideration.

That the auricular appendage can be contour forming without giving another trace in the electrokymogram than the negative auriculosystolic wave, indicates a case of total block (Fig. 11). On the curve over the left ventricular contour there is, as there should be, a rising wave at every P wave on the electrocardiogram. More cranially at the passage between the ventricle and the pulmonary artery there is still the main ventricular movement, but every P wave is now followed by a negative wave on the electrokymogram, which can hardly mean other than that a part of the auricle is contour forming here.

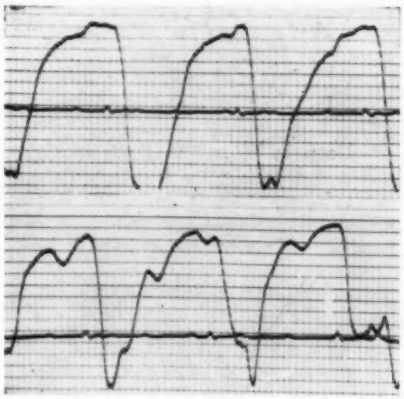

Fig. 11. Electrokymogram from a case of total block. Upper is from the left ventricle, lower from the region of the left auricular appendage. Refer to the text.

These examinations have thus produced the following results:

1) that typical auricular movements could be recorded in 45 out of 50 cases in the region of the left auricular appendage.

2) that in most of these 45 cases no contour of the auricular appendage could be delimited on a frontal radiogram.

3) that in 5 cases no certain auricular movements could be observed over the region of the left auricular appendage. It was not possible in any of these cases to observe any contour of the auricular appendage on the frontal radiogram. This indicates that the auricular appendage should not be contour forming in every case, or that it is contour forming in so small an area that its movements escaped being recorded.

4) no uncharacteristic movements have been obtained in the area in question.

SUMMARY

In the literature there are a number of different reports of the movements of the auricular appendage. The author has examined the area of the left auricular appendage with electrokymography in 50 cases. It was possible in most of these to record typical auricular movements in the region of the auricular appendage, even if no contour of the auricular appendage could be observed on a frontal radiogram.

ZUSAMMENFASSUNG

Im Schrifttum liegen verschiedene Angaben über die Bewegungen der Herzohren vor. Verf. hat an 50 Fällen das Gebiet des linken Herzohrs mittels Elektrokymographie

untersucht. Bei der Mehrzahl dieser Fälle liessen sich im Gebiet des Herzohrs typische Vorhofsbewegungen feststellen, auch wenn in der Sagittalaufnahme keine Herzohrkontur zu beobachten war.

RÉSUMÉ

Dans la littérature on trouve un certain nombre de données touchant les mouvements des oreillettes. L'auteur, dans 50 cas, a examiné la région de l'oreillette gauche par l'électrokymographie. Dans la plupart de ces cas il a pu enregistrer des mouvements vestibulaires typiques dans la région de l'oreillette, même lorsqu'il n'était pas possible d'observer les contours de l'oreillette sur l'image radiologique frontale.

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FROM THE ROENTGENDIAGNOSTIC DEPARTMENT I (CHIEF: GÖSTA RUNSTRÖM, M. D.) AND THE SURGICAL DEPT. I (CHIEF: EINAR LJUNGGREN, M. D.) OF SAHLGREN'S HOSPITAL, GOTHENBURG, SWEDEN.

FOCAL EXCLUSIONS IN RENAL TUBERCULOSIS[1]

by

Roland Gay

Occasionally in typical cases of renal tuberculosis all the symptoms disappear. Urinary trouble and pyuria cease, on culture the urine is sterile, and guinea-pig inoculation gives a negative result; all signs suggestive of recovery. A permanent healing of an ulcero-cavernous tuberculosis with a cicatrization of all the invaded tissues and a total disappearance of the tuberculosis process without any subsequent renal dysfunction is, however, believed to be an extreme rarity, and only few instances of restitutio ad integrum have been reported (CASTAIGNE, WILDBOLZ, KÜSS-GOUYGOU). As a rule the cessation of the symptoms is due only to a so-called »exclusion», *i. e.* the tuberculous foci are sealed off from the urinary tract.

Tuberculosis of kidney may run either of two courses: (1) terminating in caseation, which is the most common development, (2) terminating in cicatrization (WILDBOLZ, CIBERT). The disease may proceed with varying rapidity and intensity depending upon the varying activity of the process (KÜSS). Thus, some cases run a rapid course with extensive cavity formation, others run a very slow and less ravaging course, whilst other types, to which belong the fistulo-cavernous cases occasionally met with in the routine examination of the kidney in genital tuberculosis in men, are quiescent for long periods (CHEVASSU).

There are also a number of intermediary forms, in which exclusions are of certain interest. In cases with exclusions the focus is sealed off from its surroundings and is no longer able to pour its purulent and infectious discharge into the urine. Total and partial exclusion are distinguishable.

Total exclusion is caused by obliteration along a varying length of the ureter. The kidney may become hard or fluctuating, and its surface

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is often studded. In the final stage pyonephrosis or a total »putty kidney» develops or, though less frequently, tuberculous hydronephrosis follows. In partial exclusions the tuberculous foci are sealed off by an obliteration of the calyx or of a group of calyces draining the lesion. In this form of exclusion, as in the total form, the sealed-off process undergoes a number of changes in course of time. Partial exclusion may thus result in: partial »putty kidney», partial pyonephrosis, or hydronephrosis. The disease may also run other courses in which the process may become cyst-like with cavity formation in the parenchyma, »les poches claires» of the French. As a rule the cavities are solitary, seldom multiple. Partial exclusions may occur isolated or in association with other tuberculous changes in the kidney.

The consequence of these exclusions varies. In some cases the process is quiescent or inactive for long periods, as may be witnessed in post mortem examinations of elderly patients who died from diseases not related to the renal affection. Occasionally a complete healing of the tuberculous process is seen, in other cases latency is but transient; after some time new foci form, the process spreads and seeks a new outlet by ulcerating elsewhere into the renal pelvis, and tubercle bacilli are again eliminated. Bacilli have been demonstrated in the material accumulated in »putty-kidneys» (TUFFIER, BONNEAU) and in the fluid in the so called »poches claires» (HEITZ, BOYER). In such cases the sealed or closed process constitutes a latent threat: »Le rein exclu n'est donc pas rein guéri» (CIBERT).

Total exclusion is not infrequent and has surely been observed by most surgeons and roentgenologists, whereas partial exclusions are more uncommon and therefore more sparsely reported (CHEVASSU 1938 estimated the proportion of incomplete exclusions to complete to be 4 : 10). The term exclusion is, however, not new. Already in 1903 LE FUR described two cases. Cases have also been published by: HEITZ-BOYER (1912 and 1914), ALESSANDRI (1914), GAUTHIER (1921), WILDBOLZ (1925 and 1933), MICHON (1925), JUNGANO (1926), BOECKEL and FRANK (1928), CHEVASSU (1935), SCHAFFHAUSER (1935), LJUNGGREN (1941), OLLE OLSSON (1943), CIBERT (1946), KÜSS (1947).

In LJUNGGREN's tuberculosis material at the Surgical Dept. I Sahlgren's Hospital, most cases of which were examined at the Roentgen Dept. I, five cases of partial exclusion have been met with during the last year. These cases will be described in the following. The first four cases are interesting for the roentgenologist because the patients were roentgen examined both before and after exclusion. The fifth case was one with a partial exclusion in a tuberculous kidney with calcifications in the parenchyma outside of the amputation border. Finally a report will be given of a 6th case with bilateral incomplete exclusions.

Fig. 1.

Fig. 2.

Fig. 3.

Case I. Male. Born 1916.

In 1943 pat. was treated at Sahlgren's Hospital for epididymitis ac. dxt. No elimination of tubercle bacilli. *Excretory urography:* Kidneys of usual form and size. No calcifications. Left pelvis normal findings. Right pelvis could not be studied closely because it was masked by intestinal contents. *Right retrograde pyelography:* Renal pelvis exhibited no abnormalities (Fig. 1). In 1948 pat. was re-admitted for: Epididymitis, spermatocystitis et prostatitis tuberculosa cum fistula reg. inguinal. dx. *Excretory urography 17th April 1948:* Left pelvis: normal findings. In the right kidney (Fig. 2) the outline of a cranio-laterally directed minor calyx belonging to the superior calyx-group was abnormal, the stem tapering off conically and no contrast filling being observed at the site of its cup. This cup was manifest in the urogram taken in 1943 (Fig. 1, arrow). Immediately lateral to the apex of the conical stem was a round, slightly opaque spot, half the size of a pea. Cavity? (Fig. 2, arrows).

Patient was transferred to Rävlanda Sanatorium. In April 1948 Pas-cure[1] was initiated. Guinea-pig inoculation gave a positive result in May 1948. Since June 1948 all guinea-pig inoculations have given negative results. *Follow-up excretory urography. Dec. 1948.* No roentgen evidence of intra-renal calcifications was discerned. Left pelvis: normal findings. Right pelvis: the stem of the cranio-laterally directed calyx was still conical and sharply outlined. No opacity was observed outside the apex (Fig. 3, arrow).

Summary of roentgen findings:

1943 (Fig. 1). No urographic evidence of abnormality. April 1948 (Fig. 2): exclusion of a cranio-laterally directed calyx in the proximal calyx-group. A small cavity outside the apex (dots). Dec. 1948 (Fig. 3). Definite exclusion. No cavity filled.

Thus: *exclusion of an isolated calyx-cup.*

[1] Paraaminosalicylic acid.

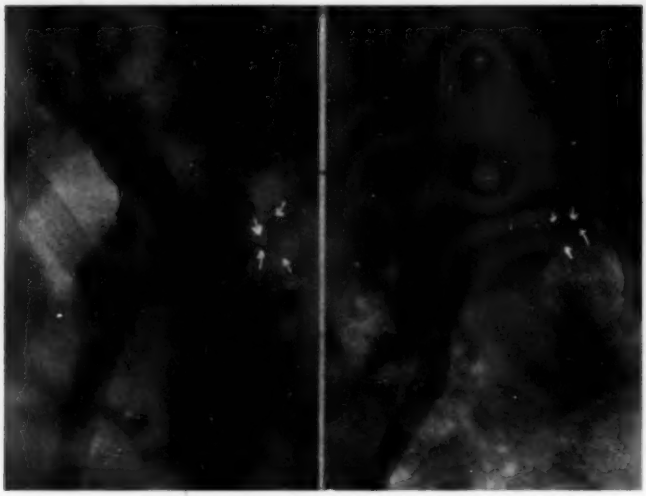

Fig. 4. Fig. 5.

Case II. Woman. Born 1903.

Tuberculosis of the lungs was diagnosed in 1926. 1933, radiogram of the lungs: tuberculous changes of long standing. No signs of activity. 1935, St. Erik's Hospital: Pains in the lumbar region and symptoms of cystitis. Guinea-pig inoculation gave a positive result. *Excretory urography 1935:* No excretion from left kidney. In the right kidney the outline of one of the inferior calyces was irregular. *Left retrograde pyelography:* Left kidney was enlarged and the pelvis grossly deformed, probably destruction of the parenchyma (tuberculosis?). Left nephrectomy was done. Anatomico-pathological diagnosis: tuberculosis. 1944, St. Erik's Hospital. *Excretory urography:* Right kidney: the outline of the cup of one of the middle calyces was distorted and somewhat ragged (Fig. 4, arrows).

1945, Garnison Hospital, Stockholm. *Excretory urography:* The destruction of one of the middle calyces described in the previous urographic exam. had progressed and no filling was now seen in the calyx-cup. The stem of the calyx tapered off evenly (Fig. 5, arrows). In addition hereto, a cavity half the size of a pea was seen outside one of the most inferior calyces. Guinea-pig inoculation gave a positive result.

1946. Symptoms of cystitis and the urine gave a positive reaction in guinea-pigs.

1947. Allmänna BB., Stockholm. Tuberculous salpingitis. Guinea-pig inoculation gave a negative result: *Excretory urography:* The picture of the excluded middle calyx was unchanged. Outline still even (Fig. 6, arrow). The cavity adjacent one of the inferior calyces had changed in shape and now consisted of two very small cavities. There was also a small cavity outside one of the most superior calyces, whose outline was ragged.

1948. Sahlgren's Hospital. General condition of the patient was good. No cystitic discomfort. Pat. worked. *Right retrograde pyelography:* Outside the cup of the most superior calyx a radiopacity indicated the existence of an oblong, well-outlined cavity, about half the size of a pea. There was no clearcut roentgen evidence of any changes in the actual calyx-cup and the stem. The roentgenogram of the excluded middle calyx

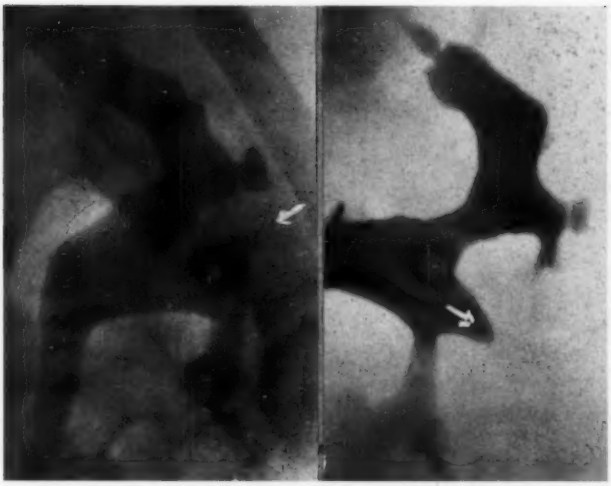

Fig. 6. Fig. 7.

previously described still displayed the same picture (Fig. 7, arrow). The cup of the most inferior calyx was of irregular shape. Outside the cup was a small, well-defined cavity.

Summary of roentgen findings:

1935, serious tuberculous changes in left kidney. Nephrectomy was carried out. The outline of one of the inferior calyces of the right kidney was somewhat irregular. 1944 (Fig. 4): the cup of one of the middle calyces was distorted. 1945 (Fig. 5) the cup of the above-mentioned calyx was excluded, and the calyx stem now terminated conically. Adjacent most caudal calyx was a cavity half the size of a pea. 1947 (Fig. 6): the caudal cavity had changed shape and now consisted of two very small cavities. The picture of the excluded cup in the middle group of calyces was unchanged (arrow). Finally, a small cavity was seen adjacent the most superior calyx in the cranial group of calyces. 1948 (Fig. 7): the roentgen picture was on the whole unchanged but the pathologic changes were now more distinctly outlined.

Case III. Woman. Born 1917.

In 1936 treated at Sahlgren's Hospital for bilateral renal tuberculosis. Pat. had had bladder symptoms and pains in the back.

Excretory urography in 1936: kidneys of normal size and shape. The confluence of the left pelvis was narrowed because the ureter and both the cranial and caudal groups of calyces tapered off towards the confluence. Destruction in both the upper and middle

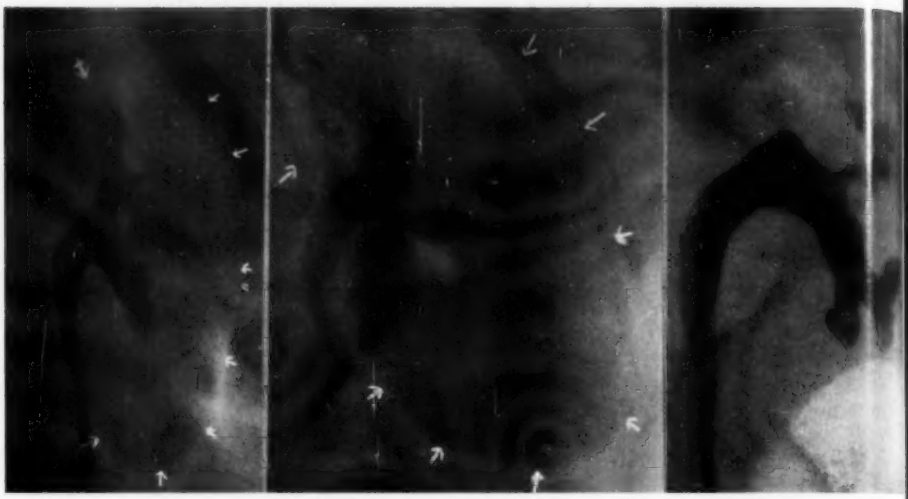

Fig. 8. Fig. 9. Fig. 10.

calyces. On the right side the outline of the upper calyx group was ragged and there was a cavity half the size of pea (Fig. 8, arrow).

Left nephrectomy was done. Anatomico-pathological diagnosis: Renal tuberculosis. Twelve years later, in the autumn of 1948, when pat. was examined for obtaining a passport, pyuria was detected. Since 1936 pat. had had no bladder symptoms. In 1945 she had been operated on for tuberculous spondylitis. Since the spring of 1948 she had had slight stitch in the right of the back. In Nov. 1948 Dr. Ljunggren was consulted. Guinea-pig inoculation with bladder urine and right ureter urine gave positive results.

Excretory urography 1948 (Fig. 9). Caudal half of right kidney was now grossly enlarged. The whole of the upper group of calyces was auto-amputated on a level with the border between the upper and lower calyx-groups. The amputation border was rounded off and even. The calyces of the lower calyx-group were somewhat wider than before but exhibited no definite roentgen evidence of destruction. At the site of the calyx that was found lateral to and immediately below the point of division of the calyx-groups in the previous examination there extended an opaque streak, 1 cm. long and 0.5 cm. wide, terminating in an irregular cavity somewhat larger than a pea. *Retrograde pyelography* was made some days later (Fig. 10). Status unchanged.

Summary of roentgen findings:

In 1936 widespread tuberculous changes in left kidney (nephrectomy). The border of the superior calyces of the right kidney was jagged (Fig. 8) and evidence of a cavity was seen (arrow). In 1948 (Figs. 9 and 10): Caudal half of the kidney enlarged. Upper calyx-group was auto-amputated at base. Amputation border was rounded off and even. The lower calyces were slightly dilated, no destruction. Contrast filling of a caval

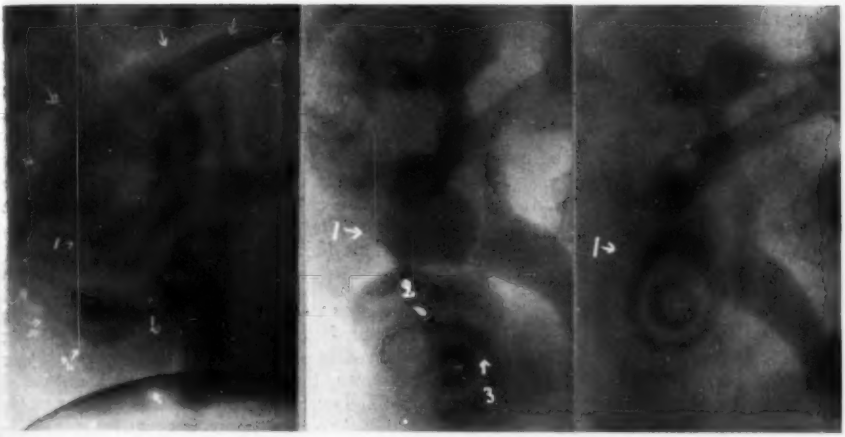

Fig. 11. Fig. 12. Fig. 13.

1 cm. long extending from the upper part of the remaining pelvis. The canal terminated in an irregularly shaped cavity, somewhat larger than a pea.

Thus: *exclusion of a whole group of calyces.*

Case IV. Woman. Born 1906.

In 1946 pat. was operated for tuberculous salpingitis. Autumn 1947 pains in the small of the back, bladder symptoms and hematuria. There was loss of weight. Pyuria.

Admitted to Sahlgren's Hospital in Dec. 1947. Radiogram of the lungs: a few thin streaks ascending from left hilum up towards the apex of the lung. No signs of active process.

Excretory urography on 19th Dec. 1947 (Fig 11): Right kidney of usual shape. Left kidney was relatively larger and of irregular shape with an indentation of the outline of the caudal part. No evidence of changes was observed in the right pelvis. The left renal pelvis was somewhat dilated. At the base of the stem of the lower calyx-group there was partial stenosis with an irregular outline (a and b). From (a) there extended a fine streak to a dilated and deformed upper calyx in this group (1). Inferior to this group, on a level with the identation of the outer contour, was a round opacity the size of a walnut (2). This opaque accumulation was in narrow communication with the renal pelvis (b). In the contrast filling (2) were irregularly shaped defects.

Cystoscopy revealed no clearcut evidence of tuberculous changes. Guinea-pig inoculation with urine from right ureter gave a negative result, from bladder urine, positive (Dec. 1947). The patient was treated alternately at Sahlgren's Hospital and Rävlanda Sanatorium with Pas. After about one month's treatment with Pas the bladder symptoms disappeared.

Excretory urography: 14th April 1948 (Fig. 12): No further change in the shape of the kidneys. No calcifications. Still no changes in the right renal pelvis. On left side no

change in the stenosis at the base of stem of the lower calyx-group. Dilatation and deformation of the upper calyx of this group (1) had increased. The opacity (2) was of the same shape. The contrast defects were, however, more distinct. Another round contrast deposit (3) somewhat below and medial to (2) was now seen. Repeated guinea-pig inoculation gave positive results. Pat. increased in weight and her general condition was good. An *Excretory urography* was made on 11th Aug. 1948 (Fig. 13): No definite changes in right side. On the left side the two distal contrast deposits (Fig. 12: 2 and 3) were no longer present, probably due to stricture of the calyx stem now being complete. The proximal cavity (1) was apparently unchanged. Otherwise, no more new changes were observed.

On 2nd Sept. 1948 nephrectomy sin. was done (Ljunggren).

Anatomico-pathological diagnosis (Fig. 14):

Gross findings: Kidney of usual size. No changes were seen in the upper half of the kidney except that the caudal calyces were somewhat wide. The lowest major calyx entered funnel-like into the lower part of the ampulla of the pelvis. This calyx major bifurcated into what were apparently minor calyces, the lower one of which extended in a lateral direction, the other, dorso-laterally. The lower branch, which was very narrow and permitted the passage only of a fine sound, led to a cavity which was incompletely divided. This cavity was lined with a 1 mm. thick layer of greyish-yellow tissue, and at some places it was separated from the outer surface of the kidney only by a 3 mm. thick layer of parenchyma containing a number of greyish tubercles. The upper branch (minor calyx), which was about as thick as a knitting needle, entered a cystic formation the size of a hazel-nut (not visible in Fig. 14) and with a practically smooth wall. In the lower pole of the kidney there was a cherry-sized, smooth-walled cyst without any apparent connection to the renal pelvis. The mucous membrane lining the renal pelvis was rather thin, pale, and smooth without any distinguishing tubercles.

Microscopic examination:

The above-mentioned cavity was covered with a thin layer of caseous material. Under this layer were isolated patches of granulation tissue of histologically unspecific appearance but with tendency to fibrosis. At other sites the caseous layer was bordered by a row of radial epitheloid cells with a few isolated giant cells. At their base the specific granulations formed a young connective tissue, patches of which were abundantly infiltrated with lymphocytes. The renal parenchyma adjacent the cavity was very atrophic. There remained only a few glomeruli, most of which were hyalinized. In the stroma, in which rich round-cell infiltration was to be seen, there were not only isolated channels but also well defined small and large tubercles. These tubercles consisted mainly of epitheloid cells. Caseous necrosis of the tubercles was seen only in a few isolated patches.

Many of the tubercles displayed more or less marked fibrosis. The caudal cyst closed to the renal pelvis was covered with a thin layer of transitional epithelium. Under this epithelial investment the loose fibrous tissue was invaded by lymphocytes and isolated tubercles. The tubercles consisted of epitheloid cells with a few Langhan's cells. *There was no caseous necrosis in the tubercles.* The picture of the upper cystic formation in the caudal half of the kidney was in principle the same as that just described.

No mucous membrane structures were seen in the lower major calyx or the minor calyx emptying into it. The channel was lined with tuberculous granulation tissue, consisting mainly of epitheloid cells and lymphocytes. In the granulation tissue a few isolated Langhan's cells and signs of commencing necrosis in those parts facing the lumen. *In some patches there was a marked tendency towards fibrosis.*

The cystic formations described above were evidently cystic minor calyces, »calyx cysts», the expression of a local hydronephrosis. Changes suggestive of hydronephrotic renal shrinkage with some hyalinized glomeruli and small groups of cystic-like wide channels were seen in the surrounding renal parenchyma.

No tuberculous changes were detected in the other parts of the renal parenchyma examined. Except for a number of epithelioid cell tubercles without caseous necrosis in the mucous membrane of the renal pelvis immediately at the funnel-like mouth of the lowermost major calyx, no tuberculous structures were discovered in the renal pelvis. There were no tubercles in the stump of the ureter. The sub-epithelial tissue lining the renal pelvis and the ureter were poor in cells and somewhat fibrotic.

Fig. 14.

Anatomico-pathological diagnosis: Tuberculosis localized to the lower part of the kidney and neighbouring portion of the renal pelvis. The histological picture was suggestive of a certain healing tendency in the form of partial fibrosis of the tuberculous granulation tissue (HILD HANSSON, HAMPERT).

Summary of roentgen findings (fig. 15):

December 1947: Right kidney apparently normal. Left kidney (Fig. 11) was of irregular shape with an indentation of the outline of the caudal portion. All the calyces were slightly dilated and ill-shaped. At the base

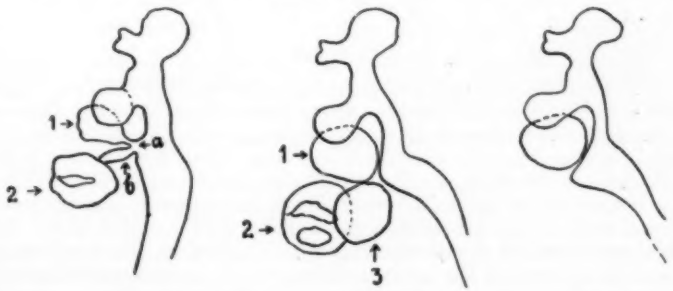

Fig. 15.

Fig. 16.

of the lower calyx-group there was a partial stenosis with irregular outline (a and b). From a) there extended a fine channel to an upper dilated and deformed calyx (1). Inferior to this deformed calyx and on a level with the indentation of the outer contour a walnut-sized round opacity (2). This opacity was connected with the renal pelvis via a fine channel (b). In the contrast accumulation (2) were ragged defects. April 1948 (Fig. 12) partial stenosis unchanged. Contrast deposit (1) had increased. Nr. 2 was still of the same shape. Appearance of a new cavity (3) below and medial to 2. Aug. 1948 (Fig. 13): Stenosis now complete. No filling of the lower opacities (2 and 3) seen earlier.

Case V. Woman. Born 1901.

Since the beginning of Jan. 1948 pat. had had pains in the small of the back and bladder discomfort. Pyuria. *Excretory urography* 24th Feb. 1948 (Fig. 16): Right kidney presented a normal picture. Left kidney: upper pole enlarged, lateral outline somewhat irregular. Somewhat above the middle of the kidney, about half a centimetre short of the outer cortical border, was evidence of a calcification about the size of a walnut (1) in the parenchyma. On the right side the upper calyx group was slightly dilated and the outline was not well demarcated. The other calyces were apparently normal. On the left side the lower calyx group showed no abnormalities. No contrast medium entered the upper calyx group because it was autoamputated at the base. The amputation border was rounded off and smooth. The lateral superior part of the renal confluence terminated conically (2). Lateral to the apex was a pea-sized, round, and sharply defined contrast filling. Lateral hereto was a dilated, oblong calyx (3) with an upper concave border, in

Fig. 17.

which the above-mentioned walnut-shaped calcification in the parenchyma seemed to fit or rest. Culture from bladder urine 1st March 1948: Tubercle bacilli. The pat. was cared for alternately at Sahlgren's Hospital and Rävlanda Sanatorium. From March 1948, she was treated inter alia with Pas. Since April 1948 she had been free of bladder symptoms, and repeated guinea-pig inoculation and culture gave negative results. Pat. was reviewed urographically on 4th Sept. 1948 and 4th Feb. 1949 but no changes in her condition could be detected.

Summary of roentgen findings.

Feb. 1948 (Fig. 16): complete exclusion of the entire upper calyx group in the left kidney. Upper lateral part of the confluence of the left renal pelvis was conical. Outside the apex was a pea-sized, round, well-defined contrast filling. Lateral to this filling was a dilated and deformed calyx with a concave upper border. Immediately over the concavity was a walnut-sized calcification in the parenchyma. Lower group: normal picture. On the right side the upper calyx group was slightly dilated. No destruction. *Urographic review* Sept. 1948 and Feb. 1949: status unchanged.

Case VI. Male. Born 1921.

In 1940 pat. was treated at Sahlgren's Hospital for left renal tuberculosis, he had severe bladder symptoms.

Excretory urography 7th March 1940 (Fig. 17): Right kidney presented the usual picture. Left kidney: enlarged and of irregular form. Upper calyx group was auto-am-

Fig. 18. Fig. 19.

putated at base, whose border was now round and even. The lower calyx group was slightly dilated and one of the upper calyces in this group was deformed.

Cystoscopy: edematous and moderately red mucous membrane. No clearcut evidence of tuberculous changes.

Left retrograde pyelography (10th March): Status unchanged. Culture (10th March) from bladder urine and left urether urine: sparse tubercle bacilli. Urine from right ureter: No tubercle bacilli. 12th March 1940: Nephrectomy sin. Anatomico-pathological diagnosis: Cavernous tuberculosis in the entire upper part of the kidney. 1941 Follow-up exam.: no bladder symptoms. Urine contained an abundance of white cells and tubercle bacilli. 5th March 1941: Excretory urographic exam. (Fig. 18). Right kidney of same form as before. Immediately above one of the middle calyces was a broom-stick-like streak of contrast medium extending latero-cranially into the parenchyma (1). The picture was otherwise apparently normal. 1942. Sahlgren's Hosp.: tuberculous epididymitis. Epididymectomy. In 1944 the bladder symptoms became more marked. Hematuria. Pyuria. Culture from urine: abundant tubercle bacilli.

Excretory urography 21st March 1944, but the shadows were too weak to permit a detailed evaluation of the picture although a considerable thickening of the bladder wall was observed.

Retrograde right pyelography 9th June 1944 (Fig. 19): Above one of the middle calyces at the site of the pathologic contrast streak of 1941, there was now a ragged opacity the size of a bean (1). Cavity? Inferior to this middle calyx there was in 1941 a normal calyx which was now destroyed and indicated only by a few narrow irregular contrast streaks (2). Finally, the base of the undermost calyx was now extremely narrow (2 arrows). The outline of the actual cup was somewhat irregular. 1945: increasing discomfort from cystitis. The ureter was transplanted ad modum Coffey. One week later the patient died from uremia. *Post mortem examination:* Left kidney: In the lower part of the left kidney was a cavern filled with caseous material (further details unavailable).

Summary of roentgen findings.

March 1940 (Fig. 17): exclusion of upper calyx-group in left kidney. Even auto-amputation border. No changes in right side. *Left retrograde pyelography:* status unchanged (nephrectomy sin.). 1941 (Fig. 18): above one of the middle calyces there was a brush-like opacity extending laterally into the parenchyma (1). The picture contained no other abnormalities. *Right retrograde pyelography* 1944 (Fig. 19): at the site of the contrast streak seen in 1941 there was now a bean-sized filling defect with a ragged outline (1). Destruction of a calyx normal in 1941 (2). Finally, extreme stenosis of the stem of the lowermost calyx (2. arrows), whose outline was somewhat irregular.

General Summary of the Roentgen Findings in Partial Exclusion

A small tuberculous process, extending, for example, from a solitary papilla is capable of deforming a calyx cup, whose outline will then become irregular and jagged, and contrast filling of a cavity is sometimes seen. If the fibrous component is predominant, the tuberculous process and its environment will shrink. This will seal the stem of the calyx, which will then terminate conically and often with an even outline (Cases I and II). Owing to the fact that the stem tapers off so evenly, such small changes are liable to escape detection. Ragged outlines, even though the raggedness is but slight, are discovered much easier.

The recognition of such changes is still more difficult if the even amputation of a calyx is so complete that the roentgen-anatomical picture seems to be normal (Olle Olsson). Comparative urograms from earlier examinations which might facilitate the discovery of abnormalities are not often available. A comparison with the renal pelvis of the other kidney may at times give rise to suspicion, provided of course that both pelvises are practically of the same shape, and that the distribution of the calyces is more or less equal in both kidneys. A possible calcification in the parenchyma outside a suspected portion of the pelvis is also suggestive of an exclusion.

Auto-amputation is very probably at an early stage partly ascribable to the pressure of the edema around the tuberculous process. This pressure probably fluctuates, with the consequence that the sealing off of the focus may very well vary before it is definitively sclerotized (Schneider, cited by Olle Olsson). If the pressure decreases, the stem will expand somewhat, and vice versa. This might have been the case, for example, in Case IV (Figs. 11, 12 and 13). The most distal calyx cyst (3) was not filled with contrast medium in Dec. 1947, but very well in April 1948, but only to disappear again in Aug. 1948, when the passage was obstructed by a definitive sclerosis. The transient obstruction in Dec. 1947 may have been

due to increased edematous pressure. This also applies to cavity (2), which was not filled with contrast medium at the last roentgen examination but in which an examination of the extirpated kidney revealed a fine passage between the cavity and the renal pelvis. Judging by these cases, one should therefore be very critical in the evaluation of these roentgen findings and not establish the diagnosis »complete stricture» on the basis of a single examination.

If the tuberculous process is more extensive, a possible shrinkage will lead to a more widespread exclusion. The result will be the amputation of one or more groups of calyces (Cases III—VI). In these cases the roentgenologic diagnosis is not very difficult. Here, too, the rounded border at the site of amputation is conspicuous.

As pointed out by Olle Olsson in 1943, the primary anatomical shape of the renal pelvis plays a significant part in the development of these strictures. The greater the number of calyces and the longer and narrower the calyces are, the easier stenosis will arise.

The tuberculous process outside the stenosis is sealed off from the renal pelvis. Its presence can no longer be demonstrated in the urogram unless the old connection is re-established, or a new fistula ulcerating into the pelvis is formed or, finally, if calcifications form in the parenchyma around the stenosis.

As a rule excretory urography will give a picture distinct enough to judge the condition, provided however that the intestines are empty, that the excretion is good and that sufficient compression can be applied to the ureters. Retrograde pyelography should be applied only exceptionally as a complementary measure to urography. In addition to the risk of forcing tubercle bacilli into a healthy kidney or to cause a lesion with a miliary spread of the disease, there is another counterindication: if an exclusion is in being, it will at this early stage probably be very susceptible to injury. The fluid injected may burst the stenosis, which may then no longer be capable of completion.

Finally a few words on the significance of exclusions in the treatment of renal tuberculosis. Hitherto, apart from a few exceptions, operation has been the treatment of choice. This radical treatment, in which the kidney is removed as soon as possible after the clear establishment of the diagnosis, was based on the belief that renal tuberculosis is localized primarily to the kidney, and that the disease is initially unilateral, and on the assumption that the disease cannot heal without the complete destruction of the kidney. In recent years, however, voices have been raised advocating a more conservative and expectant treatment. This tendency will increase with increased experience of general hygienic treatment and chemo-therapeutic means — sanatorium care, Pas, streptomycin etc.

At Sahlgren's Hospital, Surg. Dept. I, no cases of renal tuberculosis are even operated on until after a varying period of chemotherapy, generally with Pas. We always endeavour to perform the operation at a time when the disease is in a less active or more quiescent phase (néphrectomie opportune, BEAUFOND). In those cases in which only slight changes are manifest in the roentgen picture and not accompanied by cystitis, nephrectomy is not resorted to immediately, the patient is given Pas or sometimes streptomycine and sanatorium treatment to find out whether the disease will not heal without surgical intervention. Nephrectomy is not done before the process shows signs of aggravation or before the appearance of cystitis. The sanatorium treatment is given at the nearby Rävlanda Sanatorium in close cooperation with the Surg. Dept. I and the Roentgenologic Dept. I of Sahlgren's Hospital. At present a number of patients are cared for there with bilateral renal tuberculosis, tuberculosis in the remaining kidney after previous nephrectomy, cases, which are otherwise inaccessible for any specific therapy (LJUNGGREN).

The purpose of roentgenology used to be solely to determine the manifest presence or absence of any process in the kidney. Nowadays, however, periodic examinations are made to determine whether the processes show any signs of healing or aggravation. One sign of healing is the above mentioned focal exclusions. One might well imagine, as pointed out by CHEVASSU, that a cavity might be capable of healing without its communication to the renal pelvis being interrupted.

In course of time and with increased experience we hope to revert to and describe in a future publication the roentgenologic criteria arguing for such a healing.

SUMMARY

The anatomico-pathological and roentgen findings made in six cases of partial exclusion in renal tuberculosis are described and discussed.

ZUSAMMENFASSUNG

Beschreibung und Diskussion der anatomo-pathologischen und röntgenologischen Befunde bei sechs Fällen von Nierentuberkulose mit partieller Exklusion.

RÉSUMÉ

Description et discussion des observations anatomo-pathologiques et roentgenologiques trouvées dans six cas de tuberculose rénale avec exclusion partielle.

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AUS DER MEDIZINISCHEN UNIVERSITÄTSKLINIK, ERLANGEN (DIREKTOR: PROF. DR. K. MATTHES) UND DEM LABORATORIUM FÜR ELEKTROMEDIZIN DER SIEMENS-REINIGER-WERKE, ERLANGEN, DEUTSCHLAND.

AUSBLICK AUF DIE ANWENDUNGSMÖGLICHKEITEN DER ELEKTRONENSCHLEUDER IN DER MEDIZIN UND BISHERIGE VERSUCHSERGEBNISSE MIT ULTRAHARTEN STRAHLUNGEN[1]

von

F. Wachsmann

Das Problem der röntgentherapeutischen Beeinflussung tiefliegender Herde führte bis in die letzte Zeit zu einer Steigerung der Strahlenhärte, um auf diese Weise in der Tiefe höhere Dosen zu erzielen. Während die relative Tiefendosis bis 200 kV steil mit der Röhrenspannung ansteigt, bringt eine weitere Erhöhung der Spannung, insbesondere bei grösseren Feldern, nur noch einen geringen Gewinn (Bild 1).

Demgegenüber ist der apparative und wirtschaftliche Aufwand derartiger »Hochvoltanlagen» ausserordentlich gross. Hierzu kommt, dass sich mit den aus Transformatoren, Ventilröhren und Kondensatoren bestehenden Röntgenapparaturen Spannungen über 1 Million

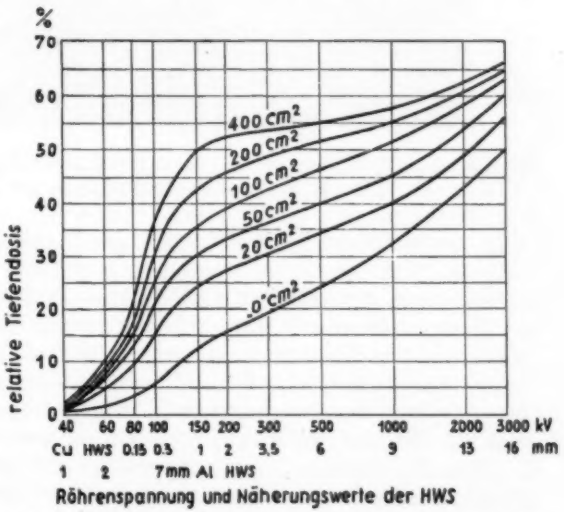


Bild 1. Relative Tiefendosis in 10 cm Tiefe bei 100 cm FHA (nach WACHSMANN (1)).

[1] Vortrag gehalten anlässlich des Nordischen Röntgen-Kongresses in Stockholm am 10. Juni 1949; bei der Red. am 13. Juni 1949 eingegangen.

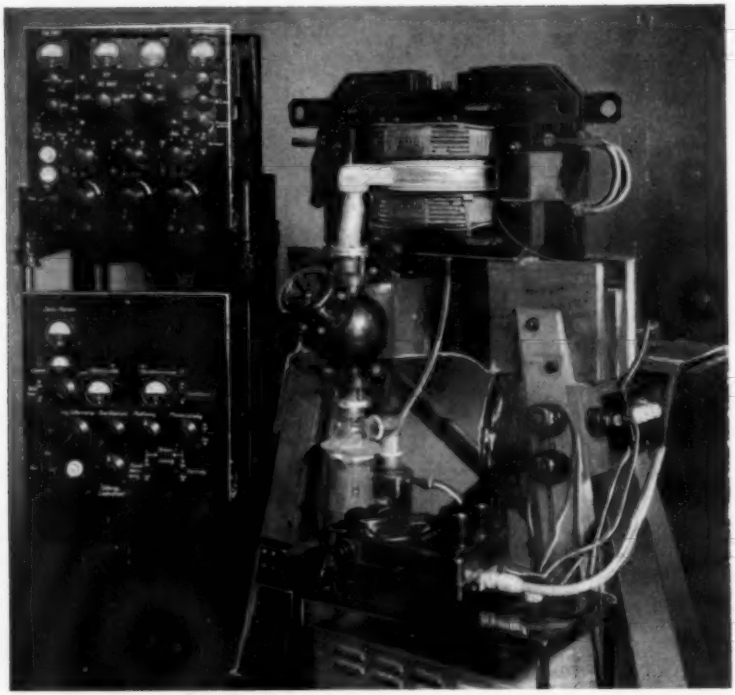


Bild 2. 6 MeV Elektronenschleuder der Siemens-Reiniger-Werke in Laboratoriumsausführung mit Bedienungselementen und Messeinrichtungen.

Volt, kaum überschreiten lassen. Auch mit den elektrostatischen Generatoren van de Graaff's können aus technischen Gründen höchstens Spannungen von 2 bis 3 MeV erreicht werden.

Erst die Beschleunigung von Elektronen im magnetischen Wirbelfeld, wie sie in der Elektronenschleuder (Betatron) erfolgt, schafft hier grundsätzlich neue Möglichkeiten. Bezüglich der Wirkungsweise dieser Apparatur sei auf die Arbeiten von KERST (2—4), WESTENDORP und CHARLTON (5), KAISER (6), GUND (7—8) u. a. verweisen.

Das Wesentliche dieser Apparatur ist jedenfalls, dass es mit ihr möglich ist, bei einem relativ geringen technischen Aufwand, Elektronen auf ausserordentlich hohe Geschwindigkeiten zu beschleunigen. Die 6 Millionen-Volt Elektronenschleuder der Siemens-Reiniger-Werke z. B. besitzt einen Transformatorkern, der nur etwa 250 kg wiegt. Auch der Aufwand an Schalt- und Regelorganen ist kaum grösser als der einer normalen Tiefentherapieapparatur für 200 kV.

Für die medizinische Anwendung von Interesse sind sowohl die von er Elektronenschleuder gelieferten Elektronen selbst als auch die bei rem Aufprall auf eine Antikathode entstehenden ultraharten Röntgenstrahlen. Betrachten wir zunächst diese: Schon eine Strahlung von 5 MeV ringt eine Erhöhung der relativen Tiefendosis in 10 cm Tiefe auf 75 %, lso auf etwa das Doppelte essen, was sich bei 200 kV reichen lässt (Bild 3). Bei löheren Energien wächst die lative Tiefendosis dann weiter an. Hervorzuheben ist aber vor allem ein Effekt, der dazu führt, dass die relative Tiefendosis bei diesen energiereichen Strahlungen von der Oberfläche nach der Tiefe zunächst nicht abfällt, sondern bis zu einer gewissen Tiefe stark ansteigt! Er ist darauf zurückzuführen, dass die im Gewebe entstehenden Compton-Elektronen bevorzugt nach vorne gerichtet sind und selbst grosse Reichweiten besitzen. Auf diese Weise wirken in den tieferen Schichten nicht nur die in diesen selbst entstehenden Elektronen, sondern auch die in den vorgelagerten Schichten ausgelösten ionisierend.

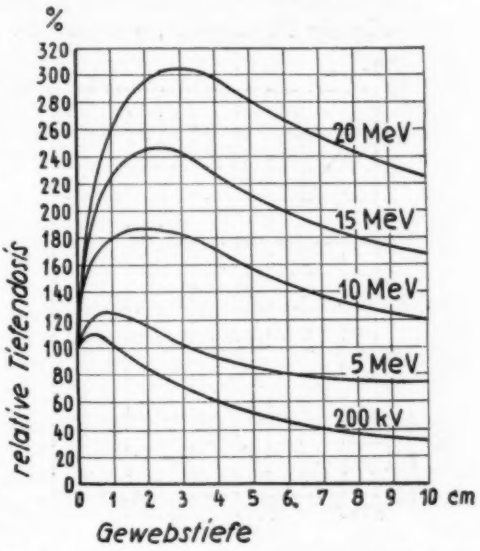


Bild 3. Relative Tiefendosen ultraharter Röntgenstrahlen von 5 bis 20 MeV (nach Koch, Kerst, und Morrison (9)) im Vergleich zu einer 200 kV-Röntgenstrahlung.

Bei höheren Energien nimmt der geschilderte Anstieg der relativen Tiefendosis ausserordentlich zu. So werden z. B. nach Messungen von Charlton und Breed (10) bei einer 100 meV-Strahlung in 10 cm Tiefe über 3,000 % relative Tiefendosis erreicht. Diese Strahlung bietet dann allerdings den Nachteil, dass bei einer Bestrahlung eines Brustfeldes die Gefahr einer Röntgenverbrennung auf dem gegenüberliegenden Rückenfeld gegeben ist. Die Anwendung derartig energiereicher Strahlungen in der Therapie ist aber auch noch aus einem anderen Grunde unvorteilhaft: Die Vorgänge in der Antikathode führen nämlich bei diesen Strahlungen dazu, dass der entstehende Röntgenstrahl mit wachsender Energie immer mehr in die Richtung der einfallenden Elektronen gebündelt wird. Dieser Erscheinung zufolge wird die homogene Ausstrahlung grösserer Felder unmöglich. Aus diesen Gründen dürfte die Anwendung gros-

ser Elektronenschleudern in der Medizin praktisch nicht in Frage kommen, ganz abgesehen davon, dass das Gewicht einer Elektronenschleuder grundsätzlich etwa mit der dritten Potenz der erreichten Endenergie anwächst. So wiegt z. B. die 100 MeV-Schleuder der General Electric 135 Tonnen.

Die Elektronenschleuder bietet aber — wie bereits angedeutet — erstmalig die Möglichkeit, die schnelle Elektronenstrahlung unmittelbar zu therapeutischen Zwecken zu verwenden. Dies war bisher wegen der geringen Reichweite weniger energiereicher Elektronen nicht möglich. Bild 4 zeigt, dass 200 kV-Elektronen im Gewebe nur $^1/_2$ mm tief eindringen. Um eine Schicht von 10 mm Dicke zu durchstrahlen sind schon Energien von wenigstens 2 Millionen Volt erforderlich, während 20 MeV Elektronen gerade noch in 10 cm Tiefe hineinreichen.

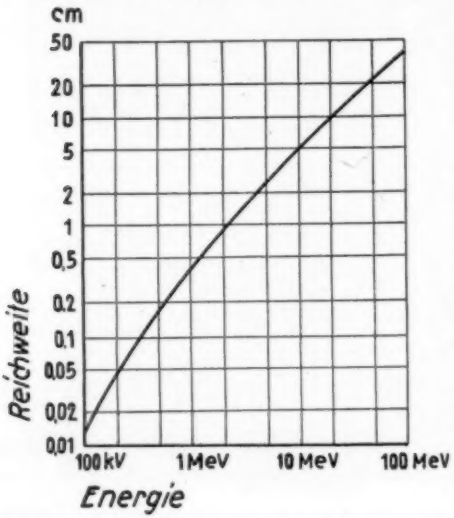


Bild 4. Grenzreichweite von Elektronen in Gewebe (Wasser).

Was die Elektronenstrahlung gegenüber der Röntgenstrahlung vor allem auszeichnet, ist der Verlauf der relativen Tiefendosis. Infolge der Gesetzmässigkeiten bei der Absorption und Streuung von schnellen Elektronen im Gewebe kommt es nämlich nicht wie bei der Röntgenstrahlung zu einem im Grundtyp exponentiellen Abfall der Dosis nach der Tiefe, sondern zu einem charakteristischen Verlauf entsprechend Bild 5: In den ersten beiden Dritteln der Eindringtiefe fällt die relative Tiefendosis bei schnellen Elektronen zunächst nicht unter den Oberflächenwert ab; sie steigt hier vielmehr je nach der verwendeten Energie und Feldgrösse auf Werte an, die etwa 30 % oder mehr über dem Oberflächenwert liegen.

In dem letzten Drittel der Reichweite fällt dann die relative Tiefendosis steil bis zum Wert 0 ab! Die Elektronenstrahlung ermöglicht es also in idealer Weise gewisse durch die angewandte Elektronenenergie in ihrer Dicke vorbestimmte Schichten angenähert homogen zu durchstrahlen und darunterliegende gesunde Gewebe zu schonen. Aus diesem Grunde sind wir überzeugt, dass die Elektronenstrahlung bei der Behandlung oberflächlicher oder direkt zugänglicher Tumoren bessere Voraus-

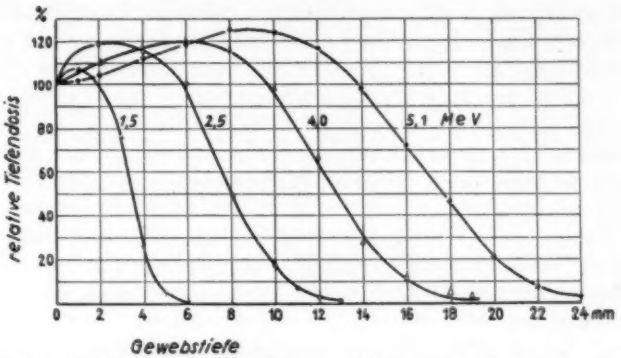


Bild 5. Relative Tiefendosen von Elektronenstrahlungen zwischen 1.5 und 5.1 MeV im Gewebe bei grossen Feldern (nach Messungen von GUND und WACHSMANN (11)).

setzungen zu liefern vermag als die bisher angewandten Strahlungen. Darüber hinaus dürfte sie aber ganz allgemein auch in der Oberflächentherapie bei der Behandlung von Hauterkrankungen grundsätzlich neue Möglichkeiten schaffen.

Was die Verwendung der Elektronenstrahlung in der Tiefentherapie anbetrifft, gehen die Meinungen noch auseinander. KERST und seine Mitarbeiter erwarten angeblich auch hier, mit der Elektronenstrahlung weiter zu kommen (zitiert nach GLOCKER (12)). Wir selbst halten die Aussichten einer Tiefentherapie mit schnellen Elektronen für wenig günstig. Wird nämlich die Tiefe des Herdes gross im Vergleich zu seiner seitlichen Ausdehnung, so kommt es durch multiple Streuung der Elektronen zu einer trompetenförmigen Erweiterung des Elektronenstrahls und dadurch zu einem frühzeitigen Abfall der relativen Tiefendosis. Ganz abgesehen davon, dass zur Durchführung von Tiefentherapie (10 cm Herdtiefe), mit schnellen Elektronen Energien von wenigstens etwa 40 MeV und somit teure Apparaturen erforderlich sind, erscheinen uns vor allem die Voraussetzungen dafür grundsätzlich nicht sehr aussichtsreich.

Die von der Elektronenschleuder gelieferten Strahlungen schaffen aber nicht nur in Bezug auf die räumliche Verteilung der Dosis im Gewebe günstigere Möglichkeiten! Sie stellen uns auch vor grundsätzlich neue dosimetrische und biologische Probleme. Wenn Sie gestatten, möchte ich mir erlauben, Ihnen kurz über das Ergebnis einiger Untersuchungen zu diesen Fragen zu berichten. Was die Messungen der ultraharten Röntgenstrahlung und der schnellen Elektronen anbetrifft, so haben wir gefunden, dass diese relativ einfach sind. Die normalen Messkammern der üblichen Dosimeter, dass heisst insbesondere die Fingerhutkammern aus Luftwändematerial zeigen untereinander kaum Abweichungen. Ja selbst,

wenn Kammern aus Aluminium, Kupfer oder Blei hergestellt werden sind die Unterschiede gegenüber gleichgrossen Ionisationskammern au Luftwändematerial nicht sehr ins Gewicht fallend (maximale Abweichung nur etwa + 25 %!). Diese Beobachtungen haben uns zu dem vorläufigen Schluss veranlasst, dass man mit jeder normalen Fingerhutkammer sowohl ultraharte Röntgenstrahlung als auch schnelle Elektronenstrahlung etwa richtig messen kann. Gewisse Probleme ergeben sich allerdings bezüglich der Definition der Dosiseinheit im Bereich dieser Strahlung. Diese in kleinerem Kreise zu diskutieren, wäre sehr interessant.

Auf einen Gesichtspunkt möchte ich jedoch hinweisen, der in der medizinischen Röntgenstrahlendosimetrie meines Erachtens auch schon bisher zu wenig beachtet wurde: Die Verwendbarkeit der auf der Ionisation in Luft aufgebauten Röntgeneinheit für die Wirkungen im Gewebe beruht bekanntlich darauf, dass angenommen wird, die Wellenlängenabhängigkeit der Röntgenstrahlenabsorption in Luft und Gewebe sei gleich. Dies trifft weitgehend zu, solange das Gewebe »wasserequivalent« ist, was z. B. beim Muskel gilt. Sobald aber Gewebe durchstrahlt werden, deren effektive Atomnummern von denen der Luft stärker abweichen, ergeben sich doch beachtliche Unterschiede!

Ausgehend von einer älteren Arbeit von Mayneord (13) haben wir (14) die Absorptionsverhältnisse in Geweben, die in ihrer Zusammensetzung von Wasser stark abweichen, näher untersucht. Das Ergebnis ist in Bild 6 dargestellt. Man ersieht aus ihm, dass z. B. im Knochen bei gleichen in Röntgeneinheiten gemessenen Dosen bei einer harten Therapiestrahlung (160 kV) etwa halb so viel ionisiert wird wie bei einer weichen Diagnostikstrahlung (70 kV). Man kann aus der Abbildung aber gleichzeitig entnehmen, dass bei einer Steigerung der Strahlenhärte auf z. B. 4 MeV eine weitere Verminderung der Ionisation im Knochen um nochmals angenähert den Faktor 3 erfolgt. Hieraus ergibt sich die Möglichkeit, bei Verwendung ultraharter Strahlungen Knochen und auch Knorpel wesentlich zu entlasten. Besonders bei der Bestrahlung von Larynx-Karzinomen — bei denen die Verwendung harter Strahlungen schon immer empfohlen wurde — dürften die ultraharten Strahlungen die Gefahr der Entstehung von Knorpelnekrosen erheblich herabsetzen. Beim Fettgewebe liegen die Verhältnisse gerade umgekehrt, da die weichen Strahlungen hier nur halb so stark ionisieren wie die harten. Inwieweit sich hieraus Konsequenzen für die praktische Anwendung ultraharter Strahlungen ergeben, bleibt noch abzuwarten.

Besonderes Interesse bietet die Frage, ob und inwieweit die neuen ultraharten Strahlungen biologische Unterschiede gegenüber den bisher in der Therapie verwendeten Röntgenstrahlungen aufweisen. Wir wissen, dass die Röntgenstrahlung im Gewebe auf dem Wege über die durch sie ausgelösten Elektronen wirksam wird. Die Elektronen ionisieren im Ge-

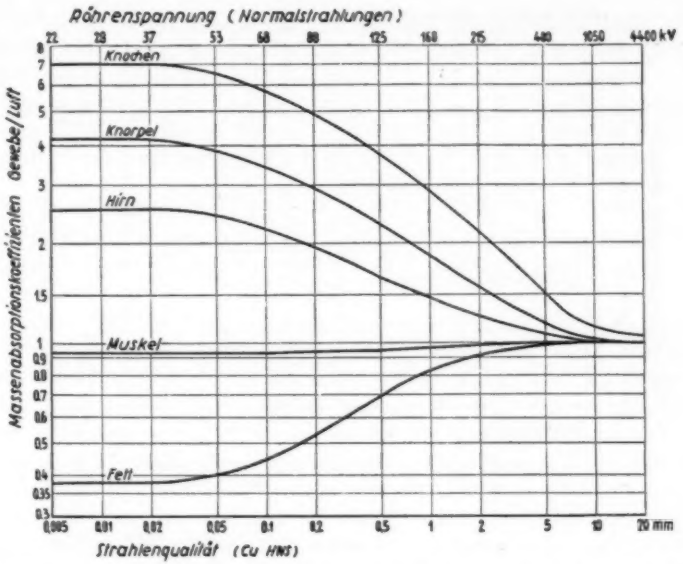


Bild 6. Ionisation in verschiedenen Geweben bei Verabreichung gleicher in Röntgeneinheiten gemessenen Dosen.

webe je nach ihrer Geschwindigkeit verschieden dicht und es ist bekannt, dass die Ionisationsdichte von Einfluss ist auf den ausgelösten biologischen Effekt.

Betrachten wir die Elektronen, die durch die bisher in der Therapie angewendeten Strahlungen im Gewebe ausgelöst werden: Bild 7 zeigt die mittlere Elektronenenergie nach Berechnungen von LEA (15) unter Verwendung der bekannten Klein-Nishina-Formel. Als Abszissen-Massstab wurde in unserer Darstellung, dem mediz nischen Verwendungszweck entsprechend, die Strahlenqualität in mm Cu-HWS gewält und die etwa erforderliche Röhrenspannung in kV oben im Bild angegeben. Da bei den weichen Strahlungen Photoprozesse vorherrschen, bei denen die Quantenenergie dem ausgelösten Elektron im ganzen übertragen wird, (abzüglich nur der bei den Stoffen niedriger Ordnungszahl, aus denen das Körpergewebe vor allem aufgebaut ist, geringen Abtrennungsarbeit!) ist die mittlere Elektronenenergie in diesem Gebiet etwa gleich der mittleren Quantenenergie der auslösenden Röntgenstrahlung. Mit wachsender Strahlenhärte nehmen aber dann die Compton-Prozesse zu, bei denen das Elektron nur einen Teil der Quantenenergie übernimmt. Hierauf ist es zurückzuführen, dass in dem weiten Gebiet der therapeutisch bisher vor

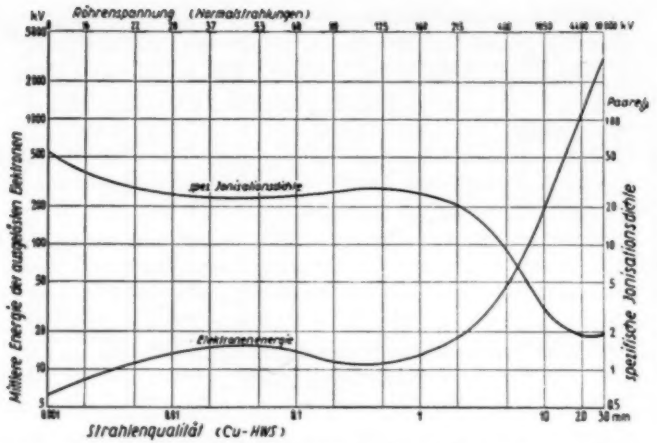


Bild 7. Mittlere Elektronenenergie und spezifische Ionisationsdichte in Wasser (Gewebe).

allem wichtigen Strahlungen von etwa 20 bis 200 kV Röhrenspannung kaum Unterschiede in der mittleren Energie der im Gewebe ausgelösten Elektronen auftreten. Entsprechend ist auch die »spezifische Ionisationsdichte», das ist die je Längeneinheit gebildete mittlere Zahl der Ionen im Gewebe, im Gebiet von 20 bis 200 kV nicht sehr verschieden! Erst oberhalb von 200 kV nimmt die Elektronenenergie mit der Strahlenqualität deutlich zu und entsprechend die spezifische Ionisationsdichte ab. Letztere erreicht zwischen 5 und 10 MeV ein Minimum, um dann wieder leicht anzusteigen (vergl. z. B. GENTNER, MAIER-LEIBNITZ und BOTHE (16)).

Aus den im vorhergehenden Abschnitt geschilderten Verhältnissen lässt sich der Schluss ziehen, dass innerhalb des Gebietes von 20 bis 200 kV Röntgenstrahlung biologische Wirkungsunterschiede physikalisch nicht zu erwarten und geradezu unmöglich sind. Die grosse Zahl der von vielen Autoren an den verschiedensten Objekten durchgeführten experimentellen Arbeiten bestätigt im grossen und ganzen diese Auffassung. Umgekehrt sind Unterschiede bei weicheren Strahlungen und ebenso beim Übergang auf Spannungen über 200 kV durchaus möglich und zu erwarten. Die weicheren Strahlungen bieten experimentell insofern ungünstige Verhältnisse als sie eine homogene Durchstrahlung der biologischen Objekte häufig nicht mehr ermöglichen. Über die Ergebnisse mit den harten Strahlungen möchte ich noch kurz berichten:

Zunächst ein Hinweis auf die bekannte Tatsache, dass bei Hochvoltanlagen, die mit 400 bis 1000 kV arbeiten, in der Regel eine geringere

Hautreaktion beobachtet wurde. Die HED (Hauterythemdosis) wird bei diesen Strahlungen allgemein etwa 1 1/2 bis 2 mal so gross angegeben wie bei Strahlungen unter 200 kV.

Bei Radium sind Untersuchungen der biologischen Wirksamkeit zwar sehr oft angestellt worden. Leider sind diese mit den mit Röntgenstrahlung erzielten Ergebnissen aber meist nicht vergleichbar, weil:

1. die räumliche Dosisverteilung sehr verschieden war und weil
2. die zeitliche Dosisverteilung infolge der bei Radium in der Regel protrahierten Verabreichungsart das Ergebnis beeinflusste.

Wir haben uns zur Aufgabe gestellt, unter streng gleichen räumlichen und zeitlichen Verabreichungsbedingungen die Wirksamkeit von Radium-Gamma-Strahlung mit der einer Röntgenstrahlung von 60 kV (Nahbestrahlung nach Chaoul) zu vergleichen. Über die dabei benützte Versuchsanordnungen und Messtechnik bin ich gern bereit, Auskunft zu geben und Kritik zu hören. Hier möchte ich nur das Ergebnis zeigen:

Zur Erzeugung von Hautreaktionen der Grössenordnung »mittleres Erythem» mussten bei Radium durchwegs etwa doppelt so grosse Dosen in der gleichen Zeit verabreicht werden, um gleiche Reaktionen auszulösen wie mit Röntgenstrahlung. Zur Erzeugung von Nekrosen der Haut da-

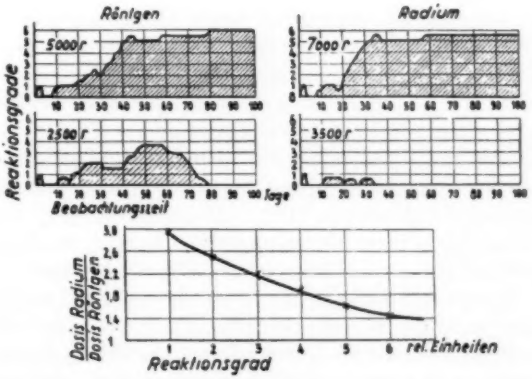


Bild 8. Oben: Zeitlicher Verlauf der Reaktionen bei der Verabreichung von Röntgen- und Radiumstrahlung verschiedener Dosis unter gleichen zeitlichen und räumlichen Bedingungen. Versuchsobjekt: Schweinehaut; die angegebenen Reaktionsgrade 1 bis 6 entsprechen der Reihe nach etwa: schwaches, mittleres, starkes Erythem, leichte und mittlere Epitheliolyse und Nekrose.

Unten: Dosis-Aequivalent Radiumstrahlung/Röntgenstrahlung bei verschiedenen Reaktionen.

gegen fanden wir an Versuchstieren bei Radium eine Dosis erforderlich, die nur etwa 1 $^1/_2$ mal so gross war wie die bei Röntgenstrahlung.

Am deutlichsten lassen sich diese Verhältnisse aus Bild 8 erkennen: Am Versuchstier Schwein wurde gefunden, dass die Zerstörungsdosis der Haut bei einmaliger Verabreichung bei Röntgenstrahlung 5,000 r., bei Radium-Gamma-Strahlung dagegen 7,000 r. beträgt. Verabreicht man nun bei beiden Strahlungen nur jeweils die Hälfte der Zerstörungsdosis, so treten bei der Röntgenstrahlung noch Reaktionen auf, die etwa dem Reaktionsgrad »starkes Erythem» entsprechen, bei Radium-Gamma-Strahlen dagegen nur eine kaum sichtbare kurz anhaltende Rötung! Allgemein kann man diese Erscheinung, die wir an verschiedenen Objekten — menschliche und tierische Haut, Erbsenwurzel, Reaktionen am Kaninchenohr und Abtötung von Kaulquappen — beobachteten, so ausdrücken, dass man sagt, der Verlauf der Dosis-Effektkurve sei bei den ultraharten Strahlungen steiler als bei normalen Röntgenstrahlen.

Wir haben gemeinsam mit v. SANDEN (17) versucht die beschriebene Erscheinung, die im älteren Schrifttum in der Regel als eine »Veränderung der Trefferzahl» beschrieben wurde, treffertheoretisch zu deuten und mathematisch zu unterbauen. Dies gelingt in Anbetracht der geringeren Ionisationsdichte der Radium-Gamma-Strahlung zwanglos. Bei der wenig dicht ionisierenden Strahlung kommt es nämlich bei Mehrtreffer-Vorgängen zu einem allmählichen Ansteigen der Ionisationen im empfindlichen Volumen aller Zellen und dann nach Erreichen der erforderlichen Trefferzahl zu einem plötzlicheren Manifestwerden des gesetzten Schadens als bei der Ionisation in grösseren Teilbeträgen.

Für die praktische Röntgentherapie besitzt das Steilerwerden der Dosis-Effektkurve eine gewisse Bedeutung, auf die hier kurz eingegangen werden soll: Die steilere Dosiseffektkurve bewirkt nämlich, dass sich bei der Radium-Gamma-Strahlung oder allgemein bei den ultraharten, wenig dicht ionisierenden Strahlungen die Wirkung dorthin konzentriert, wo grosse Dosen verabreicht wurden. Umgekehrt zeigen in diesem Falle die Stellen, die mit kleinen Dosen bestrahlt wurden, wenig oder gar keine Schädigungen. Diese Verhältnisse werden anschaulich, wenn man unter Verwendung der im Bild 8 dargestellten Dosis-Aequivalent-Kurve die Isodosen und die »Kurven gleicher biologischer Wirkungen» gegenüberstellt. Diese lassen vermuten, dass die von den Radium-Therapeuten häufig gerühmte Tumor-Elektivität des Radiums zum Teil wenigstens durch das Steilerwerden der Dosis-Effekt-Kurve zu erklären ist!

Noch eine andere Beobachtung konnten wir beim Vergleich der ultraharten Strahlungen mit den normalen Röntgenstrahlen gelegentlich machen, die vorbehaltlich gründlicher Nachprüfung hier angedeutet werden soll: Bei verschiedenen Objekten (insbesondere bei Kaulquappen) fanden wir nämlich, dass der zeitliche Verlauf der durch die beiden Strah-

narten ausgelösten biologischen Reaktionen unterschiedlich ist. Dieses usserte sich in dem Sinne, dass die mit der wenig dicht ionisierenden trahlung — in unserem Falle schnelle Elektronen — behandelten Obkte zeitlich früher reagieren als die mit der dichter ionisierenden Röntenstrahlung bestrahlten. Dies gilt auch dann, wenn die Endreaktionen i beiden Fällen etwa gleich gross waren. Ähnliche Beobachtungen wurden i n übrigen auch von LASNITZKY (18) bei der Bestrahlung von Zellkulturen mit der Beta-Strahlung von Polonium gemacht.

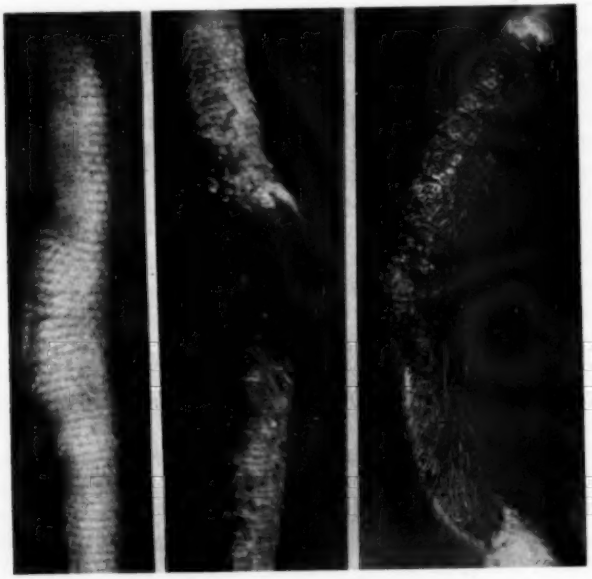
Da bekannt ist, dass die zeitliche Latenz für das Auftreten von biologischen Strahlenreaktionen weitgehend konstant und wenig abhängig von der verabreichten Dosis ist, muss diese Beobachtung zunächst verwundern. Sie lässt sich eigentlich nur durch die Annahme erklären, dass der Angriffspunkt der beiden benützten Strahlungen in den untersuchten Objekten nicht der gleiche ist. Dies liesse sich als eine »Elektivität» der ultraharten Strahlung auf gewisse Zellen oder Zellgruppen deuten, womit aber selbstverständlich noch nicht gesagt sein soll, dass die neuen Strahlungen eine elektive Wirkung etwa auf maligne Tumoren besitzen! Diese Frage muss getrennt untersucht werden.

Im folgenden sei abschiessend über Versuche berichtet, die wir (19) begonnen haben, um die Wirkung der neuen von der Elektronenschleuder gelieferten Strahlungen auf maligne Tumoren zu untersuchen. Zu diesem Zwecke überimpften wir nach einer von NIELSEN entwickelten und OVERGAARD und OKKELS (20) beschriebenen Technik ein Walker-Ca auf Rattenschwänze bezw. einen Ascites-Tumor auf die Schwänze von Mäusen. Diese Tumoren liessen sich bequem isoliert bestrahlen und beobachten, ohne den Versuchstieren im ganzen gesehen zu schaden. Die Beobachtungen bezogen sich auf die makroskopische, röntgenologische und histologische Untersuchung der Tumoren und der mitbestrahlten gesunden Gewebsteile. Registriert wurde ausserdem die Dauer der Tumorerkrankung bezw. Zeitpunkt und Dauer der Abheilung.

Diese Versuche sind noch nicht abgeschlossen. Das hier Gesagte soll somit nur die angewandte Methodik und den vorläufig gewonnenen Eindruck vermitteln. In Bild 9 sieht man zwei Serien derartiger Impftumoren die — wenn auch nicht mit gleichen Dosen gewonnen — doch in typischer Weise den Reaktionsablauf nach der Behandlung mit normalen Röntgen- bezw. schnellen Elektronenstrahlen zeigen. Wir gewinnen bei dem Vergleich der Wirkungen dieser beiden Strahlungen allgemein den Eindruck, dass die schnelle Elektronenstrahlung Vorteile bietet. Diese äussern sich einmal darin, dass die Impftumoren bei ihr in der Regel früher einschmelzen, zum anderen aber auch in einer schnelleren Abheilung der Hautreaktionen.

Schematisch sind diese Ergebnisse für die Bestrahlung mit gleichen Dosen als Mittelwerte dargestellt, die jeweils an einer kleinen Serie von

Behandlung mit Röntgenstrahlung von 0.3 mm Cu HWS.
5. 1. 49 15. 1. 49 24. 1. 49



Behandlung mit schnellen Elektronen von 5 MeV.
5. 1. 49 8. 1. 49 15. 1. 49 28. 1. 49

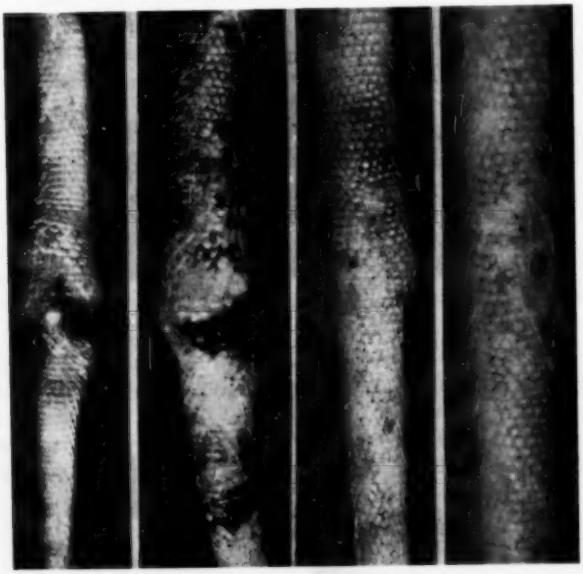


Bild 9. Serienbilder des Walker-Ca der Ratte.

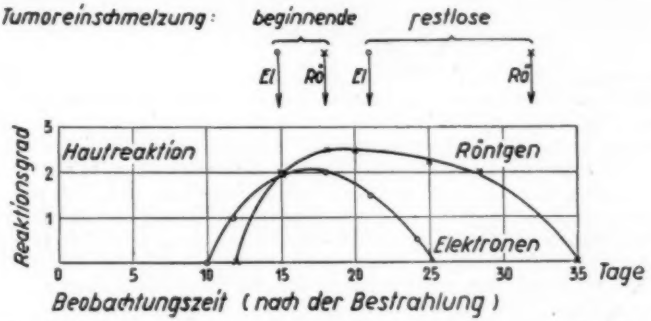


Bild 10. Graphische Auswertung der Bestrahlungsergebnisse von Impftumoren mit Röntgenstrahlung von 0.3 mm Cu HWS und schnellen Elektronen von 5 MeV: Dosis in beiden Fällen 3,000 r.

Versuchstieren gewonnen wurden (Bild 10). Es sind jedoch noch weitere Versuche erforderlich, um diese Frage mit Sicherheit beantworten zu können. Vor allem wird aber die nach sorgfältiger experimenteller Vorbereitung einsetzende praktische Anwendung der neuen Strahlungen an menschlichen Tumoren entschieden müssen, ob und inwieweit die neuen Strahlungen den bisher in der Therapie verwendeten überlegen sind.

ZUSAMMENFASSUNG

Die ultraharte Röntgenstrahlung der Elektronenschleuder gestattet eine wesentliche Steigerung der relativen Tiefendosis. Darüber hinaus kann mit Hilfe der Elektronenschleuder aber erstmalig auch die Elektronenstrahlung selbst für therapeutische Zwecke nutzbar gemacht werden. Der Verlauf der relativen Tiefendosis ist besonders günstig. Neben den Vorteilen der räumlichen Dosisverteilung sind die neuen Strahlungen aber auch noch vom dosimetrischen und biologischen Standpunkt interessant: So lässt sich z. B. mit der ultraharten Röntgenstrahlung eine starke Entlastung von Knochen und Knorpel ermöglichen. Die Dosiseffektkurven verlaufen bei den harten Strahlungen steiler und die Wirkung konzentriert sich auf die Bezirke, in denen hohe Dosen verabreicht werden. Angestellte Versuche mit Tiertumoren zeigten ein günstiges Ergebnis.

SUMMARY

The ultrahard roentgen-radiation emitting from the betatron makes a considerable increase of the relative depth dosage possible. With the help of the betatron it is furthermore possible to utilize the beam of quick electrons itself for therapeutical purposes. The distribution of the relative depth dosage is particularly favourable. Besides the advantages of the dose distribution in space the new radiation is also of interest for the dosimetric and biological considerations: Thus it was found out for instance that the ultrahard roentgen radiation effects a great relief of bones and cartilage. The curves of dosage effect are running steeper in the case of hard rays and the effects are concentrating on the fields where steep dosage gradients are used. Experiments with tumors on animals have shown favourable results.

RÉSUMÉ

Le rayonnement Rœntgen ultradur de la betatron permet d'augmenter considérablement la dose profonde relative. Mais en plus de cela on peut aussi, pour la première fois, grâce à la betatron, rendre le rayonnement électronique luimême utilisable en thérapeutique. La courbe de la dose profonde relative est particulièrement favorable. A côté de la répartition avantageuse des doses dans l'espace, le nouveau rayonnement est encore intéressant aux points de vue dosimétrique et biologique: c'est ainsi, par exemple, qu'il est possible, avec le rayonnement Rœntgen ultradur, de ménager de façon importante os et cartilages. Les courbes des doses effectives sont plus raides avec les rayonnements durs, et l'action se concentre sur les régions où sont administrées les fortes doses. Des essais entrepris sur des tumeurs d'animaux ont donné des résultats favorables.

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TESTOSTERONE PROPIONATE IN THE TREATMENT OF ADVANCED CARCINOMA OF THE BREAST[1]

by

Poul E. Andersen

It is well known that while some tumours seldom metastasize to the osseous system, others seem to have a definite, considerable affinity to the osseous tissues, an affinity which can not be easily explained as a result of the proximity of the tumour to bones, lymph vessels etc. From an endocrinological and therapeutical point of view it is especially of importance that the cancers most frequently metastasizing to the osseous system are cancer of the prostata and cancer of the female breast, tumours in organs whose development and functions are closely related to the metabolism of the sexual hormones. No wonder that one has tried to control osseous metastases from these forms of cancer by artificially producing alterations in the normal balance of sexual hormones of the organism, especially as f. e. FARROW has been able to show statistically that during the years of the natural menopause there was a noticeable decrease in the percentage of skeletal metastases in women with cancer of the breast, while a relatively high percentage occurred in the years before and after the menopause. Further FARROW & WOODARD have shown that the time interval between the primary tumour and the occurrence of bone metastases is longer in postmenopausal women than in women still menstruating.

The production of a disturbance of the estrogen/androgen hormone balance can be effected in the following 4 ways: 1) withdrawal of estrogenic, ovarian hormones, 2) addition of synthetic estrogens, 3) addition of synthetic androgens and 4) withdrawal of androgens, of which possibilities only the first 3 are of interest here and will be considered.

The first attempts at influencing bone metastases from mammary cancer hormonally were by a decrease in the estrogen content of the

[1] Read at the Meeting of the Northern Association for Medical Radiology, Stockholm, June 10—12, 1949; submitted for publication, June 21, 1949.

organism by bilateral oophorectomies, first proposed by SCHINZINGER 1889 and tried by BEATSON 1896. In 1905 LETT published 99 cases of advanced mammary cancer treated by surgical castration. He reported clinical improvement with signs of arrested growth of the cancer in about 40 % of the cases before the menopause, but no improvement in patients after the menopause.

The discovery that castration could be produced by pelvic irradiation added a more simple and less hazardous means of producing an artificial menopause and thus created the possibilities of examining the effects of the artificial menopause on the metastasizing mammary cancer. But although irradiation of the ovaries has been used extensively from about 1920, one finds only very few pure, clinical therapeutical experiments reported in the literature, the castration as a rule being combined with simultaneous local treatment of the bone lesions or other metastases. The reported results are therefore very difficult to analyze as to the effect of the produced hormonal imbalance. The reports of AHLBOM, DRESSER, MARTIN, SMITH, TAYLOR and others, however, show clearly that temporary arrest of cancer growth and recalcification of bone metastases from mammary cancer can be produced by roentgen castration. According to the experience of FARROW, a considerable improvement is obtained in 15—30 % of all cases and in about 1/3 of all premenopausal patients, manifested by a prompt relief from pain and by general physical improvement. Calcification within and around the bone metastases which according to BOUCHARD, FARROW and others is indicative of a regression, can be demonstrated radiographically in 3—6 months. As a rule the duration of the inhibition of the bone metastases is between 6 and 24 months, but varies considerably and may in rare cases (as in the case reported by CLARKSON & BARKER) be 5 years or even more. The effect seems only to be found with established bone metastases, neither TAYLOR nor ADAIR, TREVES, FARROW & SCHARNAGEL have been able to demonstrate any prophylactic action of roentgen castration.

Although a number of cases of human cancer of the breast has been reported to follow or at least appear in time after the administration of female sex hormones and although numerous experiments in both male and female animals (LACASSAGNE, LOEB et allied, and many others) have shown that administration of estrogens increases the incidence and growth of mammary cancer, several authors, especially in Great Britain during World War II (ELLIS, HADDOW, LEVITT, MCWHIRTER, PATERSON, WINDEYER, DODDS) and NATHANSON have tried to influence advanced cases of mammary cancer by administering heavy doses of estrogenic substances. The reported results were not too promising: in some cases, in women 60 years old or older, a general stimulating effect was seen with increase in weight, improvement in general physical con-

condition etc., and in a few cases shrinkage of the primary tumour, healing of cancerous ulceration, shrinkage of skin nodules, glandular and pulmonary metastases, but no radiographically demonstrable change of the bone lesions which, however, in certain cases became less painful. The favourable effect was of brief duration and the estrogenic treatment seemed in younger premenopausal women to be injurious and cancer growth-promoting if anything.

The effect on mammary cancer of a hormone imbalance produced by addition of heavy doses of androgens has not been extensively investigated till the last decennium, in part because it has not been possible to produce testosterone in the amounts demanded.

LACASSAGNE 1932, later in cooperation with RAYNAUD, and the Americans NATHANSON & ANDERVONT and others (f. e. GARDNER, HEIMAN, JONES) showed in animal experiments that administration of testosterone under proper conditions will partially inhibit the appearance of mammary cancer in a highly susceptible strain, when the animals get the testosterone at a young age while no effect was noticed on the tumour once it had developed. These experiments have later been confirmed by several authors.

1939 LOESER and ULRICH reported the first cases of mammary cancer treated by testosterone and in the last 5—6 years several reports have appeared on this subject, which seem to show that *heavy* dosage of testosterone (tst.) (emphasized by ADAIR) in some cases — FARROW says 50 % — has a certain, rather potential palliative effect. Curative effect has not been reported. Most authors have used testosterone propionate, a few testosterone acetate or methyl testosterone (BOGER, ADAIR).

During the last 2 years reports have appeared in Scandinavia too on the clinical use of tst. (LUFT, SYLVÉN & HALLBERG, KAAE).

The Effect of Testosterone

The effect of tst. administered at adequate dosage, which by several authors is reported to be about 300 mg weekly, as a rule given as intramuscular injection of 100 mg every second day — sets in after 2—3 weeks (= 600—900 mg) and consists of a striking improvement in general physical condition, increased appetite, decreased pain in the bone metastases to complete absence of pain, increasing weight, higher spirits and so on, and the patient will often be able to lead her usual life, doing housework etc. After 4—6 weeks' treatment (1,200—1,800 mg tst.) an increased density of the whole osseous system is noticed radiographically in many of the cases and especially in the areas destructed by metastases whose structure approaches the normal; beginning with a sclerotic zone around the destructed area a remineralisation takes place, at times re-

sembling callus formation and sometimes even the bone trabecles become visible. But although some local bone lesions may undergo almost complete repair as far as one can tell by radiographic study, unfortunately it happens frequently that some other bone lesion while under the same influence which is healing one bone lesion, may continue to increase and apparently not be influenced as the other lesion just as also new bone lesions may appear. It is difficult to explain why or how these patients in spite of increasing bone lesions can be without pain and in good condition with increasing weight etc., but it is seen rather often. Such intense hypercalcification — and eventually complete disappearance — of bone metastases as is sometimes seen in metastasizing prostatic cancer under estrogen therapy has never been reported and seems not obtainable.

Pulmonary metastases and other soft tissue metastases are only seldom influenced by tst. therapy, although cases have been reported showing a spectacular improvement. ADAIR, HERRMANN & ADAIR, LUFT, SYLVÉN & HALLBERG report such cases, LUFT a case in which cancerous infiltration in the side of the neck and face diminished considerably and SYLVÉN & HALLBERG report a case with retrogression of pulmonary deposits, of which some disappeared, others diminished. At the Radium Centre for Jutland, Aarhus, we too have seen 2 cases in which pulmonary deposits diminished considerably. Diminishing and sometimes even healing of cancerous ulcers has also been reported (ADAIR a. o.).

Mode of Action

The mode of action of tst. is almost unknown. It is wellknown that administration of tst. results in a positive nitrogen balance (as shown by CARTER, COHEN & SHORR and KOCHAKIAN) which can explain the gain in weight and the subjective sense of well-being. SYLVÉN & HALLBERG suggest that the mechanism of relief of bone pain might be an elevation of the threshold value for pain sensation by some central nervous action of the tst. The experiences with the treatment of angina pectoris by tst. (LESSER a. o.) together with the cardial side effects sometimes observed during the treatment of advanced cancer of the breast (acceleration of heart action etc.) seem to indicate some sympathicomimetic, nervous action of tst. FARROW mentions the possibility of a vascular action, which by the way may also be controlled by the sympathetic nerves. It is wellknown that estrogens are vasodilating, androgens vasoconstricting. Following as well roentgen castration as hormonal castration a clearly diminished vascularisation of the primary tumour and skin nodules is seen, later on followed by shrinkage. It is possible that the regression seen now and then is caused by a vasoconstriction followed by a nutritional anemia

nd fibrosis later. A few series of biopsies have been reported (HERRMANN ε ADAIR, ADAIR, FELS). In some of these were found hydropic degeneration, pycnosis of the nuclei of the cancer cells and some fibrosis around he groups of cancer cells, or only fibrosis around apparently unchanged ancer cells (FARROW), or no histologic changes at all (ADAIR). A real ytocide effect has not been reported and mitoses have still been present, if only few (HERRMANN & ADAIR). The decrease in vascularisation f the osseous metastases will also explain the recalcification of the bone esions.

Side Effects

Of course with such great amounts of tst. — most clinics and we too use about 300 mg tst. propionate a week for 10 weeks, making a total of 3,000 mg, by intramuscular injections, often followed by oral maintenance therapy by methyl tst. or by depositing therapy by crystalline tst. — must follow a considerable virilizing effect, especially in younger women. Amenorrhoea is seen in young still menstruating women, as a rule only of a few months' duration. Hirsutism is also a fairly constant reaction to androgen therapy, especially in dark-haired and -complexioned women, in whom the growth of hair over the face, lips, chest and legs is sometimes very heavy and most embarassing. Some women even have to shave almost every day. On cessation of androgen therapy hirsutism diminishes, but in some instances it may persist for many months after cessation of administration. Deepening of the voice, which becomes husky and hoarse, is also met with, especially by prolonged administration of androgen and is caused partly by a thickening of the lining membrane of the larynx, partly by a thickening of the thyroid cartilages similar to the changes taking place at puberty. An increase in libido has been reported by several authors (ABEL, HERRMANN & ADAIR, SHORR et al.) to take place at all ages below 60 years, the degree of increase varying enormously with the individual, but sometimes being quite a difficult problem to handle. Associated with this increase in sexual desire is as a rule some growth of the clitoris. Acne of the face, chest and back is also seen, but less constantly, and the condition subsides at once with the withdrawal of the hormone.

However embarassing these side effects may be, they seldom cause the cessation of the androgen therapy.

Real contraindications to the tst. treatment do not seem to exist at present. Sometimes the serum calcium of the patient is considerably increased at the beginning of the treatment. Tst. may produce a further increase, giving symptoms of hypercalcemia with nausea and vomiting and general indisposition, which may cause a cessation of the tst. treatment.

The Patients

At the Radium Centre, Aarhus, during the last year we have bee using tst. in the treatment of 30 cases of mammary cancer with meta tases, especially bone metastases. One case proved to be complicated b myelomatosis, one had shortly before been treated by heavy doses o stilbestrol and two cases had only had a single injection of tst. when som other — radiological — treatment was started. However, 26 cases ar left which have not shortly before (interval at least 4 months) or simultaneously been treated by roentgen irradiation locally or to the ovaries or by any other form of therapy which might be thought to be able to influence the effect of tst. therapy. Our treatment, as used and recommended by American authors particularly, has been 100 mg tst. propionate three times weekly by intramuscular injection for 10 weeks, followed as far as possible by 50 mg crystalline tst. once a week as a maintenance dosage. The patients were followed very carefully, control examination being made at least once a week. The blood was examined once a week with determinations of serum calcium, serum phosphorus, alkaline phosphatases, hemoglobin, precipitation rate and counts of white and red corpuscles and thrombocytes. The weight was followed, and the radiographic findings were controlled at least every fourth week. The average dose has been 2,200 mg tst. propionate, one patient was given a total of 5,000 mg, another 4,000 mg, both with excellent effect. (These great amounts of tst. were kindly placed at our disposal by »CIBA», whom we hereby give our heartfelt thanks.)

Influenced by the reports in the literature on the excellent effect of tst on bone lesions and the almost correspondingly insignificant effect on soft tissue metastases we have preferred to treat patients with bone lesions, and only treated a few patients with exclusively soft tissue metastases and no radiographically demonstrable osseous lesions. Our results correspond largely with those reported in the literature, still we can not agree that the palliative anodyne effect is as a general rule quite as striking as emphasized especially by American authors, although we too have seen instances of very remarkable improvement.

Palliative Effect

The general physical condition was improved considerably in 18 patients (69 %), while there was no or only questionable improvement in the resting 8 cases. The weight increased in 13 patients, was unchanged in 4 patients (*i. e.* inside $\pm$ 0.5 kg) and decreased in 6 patients. In 3 patients there was no control of the weight on account of their poor condition. Among 21 women who were postmenopausal, there was 16 wh

had severe pain from bone metastases and 12 of these experienced excellent relief, while 4 patients had only questionable or no improvement at all. Improvement was also seen in 2 patients in the menopause and in 1 of 2 before the menopause. Thus in all 15 of 26 patients (or 58 %) had more or less pronounced relief from pain. The alleviation began most frequently after a dosage of 600—700 mg, sometimes even earlier; in one case effect was noticed by the patient after a dose of only 75 mg. In a few cases bone pain increased during the first week or two of the treatment before palliation set in, and a few of the patients complained of more pain the days when the injections were given. The palliation persisted as long as the tst. was administered and as a rule for some time — 3—4 weeks — after the cessation of treatment and was in some cases quite amazing.

Marked reparatory changes of the bone metastases were seen in 4 cases and in 3 more cases the bone lesions did not show progression at all, while the bone system as a whole seemed to show an increased density (cp. ADAIR). In the other cases where the bone lesions have been controlled by radiographs there has not been any improvement of the skeletal metastases even if there was a good palliation of the pain, but after all thus a total of one third of our 21 patients with bone metastases showed inhibited growth or even regression of the bone lesions.

Our experiences with the effect on soft tissue metastases are not quite as good. Only in 3 patients with skin and lymph node metastases a marked shrinkage has been noticed, while in 2 cases lung metastases have been seen to decrease. In the rest of the patients no improvement of the soft tissue lesions was seen, and in three cases there even seemed to be an acceleration of the growth. In one patient neurologic spinal symptoms were markedly aggravated and in a patient with cerebral metastases the tst. treatment provoked a severe cerebral oedema. Although this was quickly relieved the neurologic symptoms had become aggravated to such a degree that tst. treatment had to be abandoned.

The usual side effects such as hirsutism, deepening of the voice, sweat, congestion of the face, acne, increased sexual desire etc. have been noticed, and in a few cases there has been nausea and vomiting on the injection days, as a rule 5—6 hours after the injection, but none of these things has indicated the cessation of treatment. In no instance a hyperthermic reaction to the used preparation was met with.

Laboratory Findings

The laboratory findings showed some interesting things. Serum calcium is said to rise by f. e. FARROW and SCHWANDER & MARVIN during tst. treatment of metastasizing mammary cancer, while ADAIR, HERR-

MANN et all., SYLVEN & HALLBERG and others have noticed a considerable fall, especially in those cases in which tst. administration is followed by clinical improvement (NATHANSON, ADAIR, ALLEN & ENGLE). We have in 16 patients followed the serum calcium through the whole treatment period and further and in 6 patients noticed a marked fall, in 6 other patients a slighter fall, in a few cases followed by a rise during the last few weeks of treatment. There was a considerable rise in the serum calcium in 4 cases, 3 of whom reacted extremely well to the tst. treatment. We have never seen those excessively high rises or deep falls in serum calcium, which have been reported in the literature (FARROW, ADAIR and others).

The serum phosphorus was followed in 20 patients through the whole treatment period and showed in 16 patients a constant fall, often to subnormal values.

The serum alkaline phosphatase level which is said (by f. e. ADAIR et all., SYLVÉN & HALLBERG) to show a rise in the cases reacting well to the tst. has also been followed regularly during the treatment. In 7 patients there was a rise, in 3 patients the value was unchanged and in 6 patients there was a fall. No safe relation between the serum alkaline phosphatase levels, the patient's condition and her reaction to the tst. therapy has been noticed in our patients, especially not between an increase in the levels and a good response to the treatment; on the contrary we noticed in one of those patients who showed the best response, a very marked fall in both of the treatment periods in which she — with 3 months' interval — was treated with tst. On the whole it is our impression that the serum alkaline phosphatase level — quite unlike the acid phosphatases in the stilbestrol therapy of prostatic cancer with bone metastases — is of no great value as an indicator of the value of the treatment. In this respect the precipitation rate is of much more value, as the precipitation rate — sometimes after an initial rise during the first injections — shows a slow, but constant decrease in all the cases which respond well to tst. The hemoglobin showed in a few cases an increase, but as a rule there was a constant decrease on account of the progression of the destruction of the bone marrow. In well over 1/4 of our patients a temporary fall in the thrombocyte count was found during the first weeks of treatment without any detectable relation to the other changes in blood values or to the response of the patient to the treatment as a whole.

Our experiences confirm the results reported by American and Scandinavian authors in the last 5—6 years to a certain extent, but we are still somewhat reserved. Certainly, the palliation, the improvement in general condition, the removal of pain etc. are of great practical and so-

cial importance to these as a rule very poor patients, but the testosterone therapy has several severe shortcomings yet; it is too expensive, it has to be given parenterally, and you can not be sure in advance that the patient will be significantly improved by the treatment. This is perhaps only a question of dosage and in all probability a more vigorous treatment will give a prompter effect and a more frequent improvement of the patients than now. But only the day when we have a powerful and cheap androgenic substance for peroral administration in sufficient quantities and with more sharply limited indications for its use, will we have a really practical and practicable androgen hormone treatment of advanced cases of mammary cancer.

SUMMARY

After a short review of the development of and experiments on treatment by castration of mammary cancer, the author reports on the effect of testosterone propionate and the results obtained in 30 cases of advanced mammary cancer. Significant palliation was obtained in about 60 % of the patients. Retardation of growth of bone lesions was seen radiographically in 33 %, while no improvement was seen in the other patients. In a few cases there was a regression of soft tissue metastases, such as lung and lymph node metastases, while in a few other cases, especially with metastases in the nerve tissue, an aggravation was noticed.

Thus the author's experiences confirm to a certain extent the results reported earlier in the literature, and the treatment with testosterone propionate seems to be of value in cases with osseous lesions in patients in not too bad general condition.

ZUSAMMENFASSUNG

Nach einem kurzen Übersicht der Entwicklung der Kastrationsbehandlung von Cancer mammae beschreibt der Verfasser die Wirkung der Testosteronbehandlung und die hierdurch erreichten Resultate in 30 vorgeschrittenen Fällen von Cancer mammae. Gute palliative Wirkung wurde in c. 60 % der Fälle gesehen. Gehemmtes Wachstum der Knochenmetastasen wurde in 33 % der Fälle erreicht, keine Besserung aber in den übrigen Fällen. In einzelnen Fällen auch Besserung der Weichteilmetastasen, sowie Schwund der Lungenmetastasen, aber in anderen Fällen, speziell bei Metastasen im Nervengewebe, wurde auch Verschlechterung beobachtet. Diese Erfahrungen bestätigen bis zu einem gewissen Grade die Resultate, die früher in der Literatur veröffentlicht sind, und die Testosteronbehandlung scheint von Wert zu sein in Fällen mit Knochenmetastasen bei nicht zu schlechtem Allgemeinbefinden.

RÉSUMÉ

Après un court aperçu des expériments et du progrès du traitement par castration chirurgicale, radiologique et hormonale, l'auteur discute du traitement par des androgènes et rapporte l'effet du traitement par le propionate de testostérone en 30 cas du cancer du sein.

En environ 60 % des cas on a obtenu une considérable amélioration temporaire de l'état général et en 33 % une retardation de la croissance des dépôts osseux. Dans quel-

ques cas on constata un effet sur des métastases cutanées et ganglionnaires et décroissance de métastases intrathoraciques. Dans deux cas de métastases nerveuses on observa une aggravation sévère.

Ainsi les assertions antérieures d'autres auteurs se confirment et on peut recommander le traitement par la testostérone pour des cas avec des dépôts osseux comme ayant un effet palliatif considérable si l'état général n'est pas trop mauvais.

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For further references see the above authors.

FROM THE ROENTGEN INSTITUTE OF OSLO TRYGDEKASSE, OSLO, NORWAY.

DYSCHONDROPLASIA [1]

Report of a Case

by

Erling Kierulf

In some instances difficulties may be involved in classifying certain affections of the bones belonging to the group dyschondroplasia. The following case is published because the peculiar roentgenological features, considered separately, may be referable to various groups of diseases.

The patient is a 21-year-old man, no. 6 of 8 children. He has one elder half-brother. They are all healthy, and so are the parents. Three of his brothers and one of his sisters have been examined. Roentgenograms of the hands and feet were normal.

The patient reports that his left little finger at the age of seven was swollen and larger than the right. At the age of 10 he noticed swelling and enlargement of the toes of the left foot. At the age of 12 the nail of the left thumb was injured and fell off later on. The nail did not grow out again as normally, and the terminal phalanx became swollen. At the age of 15 he injured his left index finger on a saw, and the terminal phalanx of this finger later on became swollen and tender. At the age of 18 he noticed some swelling immediately above the left wrist. The fingers and toes have gradually become more swollen and deformed, particularly during the last two years.

Apart from the occasion when he injured his finger at the age of 15, he has never consulted a physician.

He has been working as a truck driver, but had to give up this work as he had difficulties in loading and unloading the truck. At present he works as an electro-welder.

He was referred for roentgen examination by dr. EILER SCHIÖTZ, the physician attached to the factory.

The roentgenograms show a skeletal affection, localized to the left side, particularly to the distal parts, viz., the left hand and foot. The roentgenograms may be interpreted as Ollier's disease, enchondromatosis and cartilaginous exostoses.

In the author's opinion there is some confusion as to the classification of these diseases.

OLLIER, in 1899, described a disease which was characterized by a delayed, irregular ossification of the epiphyseal cartilage, and which he called dyschondroplasia.

WITTEK, in 1907, supplemented OLLIER's description, and defines the disease as a congenital disease due to a primary disturbance of the fetal

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Fig. 1.

Fig. 2.

Fig. 1. Enchondromatosis of the distal end of the left radius.
Fig. 2. Multiple enchondromas in the left hand.

growth of the epiphyseal cartilage, strictly confined to one side of the body at least as far as the long bones are concerned. The initial symptoms occur during early childhood.

FRANGENHEIM, in 1911, criticized the definitions given by OLLIER and WITTEK, and defined the disease as a multiple chondromatosis or enchondrosis. OLLIER's disease was merely to be considered a peculiar variety of a multiple skeletal chondromatosis.

To the author's knowledge three cases only have been published in which the demonstrable skeletal changes were strictly confined to one side (BOJESEN, Fortschritte XXIV, WEISS, Fortschritte XXI, WALTER quot. BRAILSFORD). In OLLIER's case the skeletal changes were later on proved to occur on both sides.

BENTZON's experimental investigations were aimed to prove that dyschondroplasia was a neurotrophic disease. That view is scarcely correct as analogous experiments as carried out by FALDINI and SOTO-HALL have given negative results.

LOGRÓSCINO, in 1938, demonstrated the presence of a familial con-

Fig. 3. Enchondroma localized to the anterior portion of the third left rib.

Fig. 4. Changes in the proximal portion of the left humerus showing great resemblance to a somewhat atypical cartilaginous exostosis. Note the peripheral cortical localization.

Fig. 5. Skeletal changes localized to the proximal and distal portion of the left fibula. The distal process shows great resemblance to an exostosis.

Fig. 6. Multiple enchondromas in the three lateral toes and metatarsal bones of the left foot.

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 6.

genital disturbance of the osteogenesis. In the case reported here there was an asymmetrical lumbosacral vertebra with a posterior spina bifida.

LANGENSKIÖLD, in 1947 writes that not merely the epiphyseal cartilage, but also the osteoblasts of the normal periost originate from undifferentiated connective tissue cells originally present in the epiphyseal cartilage.

Multiple cartilaginous exostoses, enchondromatosis, and OLLIER's disease are often confused. These diseases should be considered as three different manifestations of the same disease.

The etiology is obscure, but the fact that congenital chondromas exist, indicates that the disease is congenital and related to a hereditary predisposition.

In the present case, the skeletal changes are strictly confined to one side; a fact which strongly indicates a peculiar process. The changes confirm the view that OLLIER's disease, enchondromatosis, and multiple cartilaginous exostoses, are different manifestations of what may be called a dyschondroplasia.

SUMMARY

A case of a unilateral skeletal disease is reported, which confirms the view that OLLIER's disease, enchondromatosis, and multiple cartilaginous exostoses are different manifestations of a dyschondroplasia.

ZUSAMMENFASSUNG

Es wird über einen Fall von einseitiger Skelettkrankheit berichtet, der die Ansicht bestätigt, dass die OLLIER'sche Krankheit, die Enchondromatose und die multiplen knorpeligen Exostosen verschiedene Äusserungen einer Dyschondroplasie darstellen.

RÉSUMÉ

Relation d'un cas d'affection unilatérale du squelette, qui vient à l'appui de l'opinion que la maladie d'OLLIER, ou enchondromatose, et les exostoses cartilagineuses multiples sont des manifestations différentes d'une dyschondroplasie.

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FROM THE ROENTGEN DEPARTMENT OF THE UNIVERSITY HOSPITAL, OSLO, NORWAY
(CHIEF: PROF. TORLEIF DALE)

CALCIFIED DUCTUS BOTALLI PERSISTENS[1]

by

O. W. Husebye

The roentgenological findings in Ductus Botalli persistens may be characterized as indirect as the roentgenological diagnosis is made from changes observed in the configuration and size of the heart, its manner of working together with the condition of the pulmonary and hilar vessels.

In characteristic cases the findings are as follows:

1. Hypertrophy of the heart.
2. Large left ventricle.
3. Dilatation of left atrium.
4. Protuberant conus pulmonalis.
5. Increased vessels in hilum and lungs together with a large aortic arch.
6. »Hilar Dance».

Referring to the changed circulatory conditions in Ductus Botalli persistens these symptoms are fully comprehensible.

Ductus Botalli is a connection between the aortic arch and the pulmonary artery. Through this connection some blood from the aorta passes directly into the pulmonary artery instead of continuing in the aorta. The quantity of this blood, of course, is dependent on the diameter of the Ductus Botalli. In this way the pulmonary artery obtains more blood than usually, and the vessels in hilum and lungs have to increase. The »hilar dance» may be explained as pulsation from the aorta. Naturally the increased blood quantity causes dilatation of the left atrium and a hypertrophic left ventricle. Lastly, one may expect the first part of aorta down to the beginning of the Ductus Botalli persistens to be of a larger diameter than usually.

The part of the circulatory system in question may be said briefly to work with a larger quantity of blood than normally.

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It is necessary to emphasize, however, that one or more, even all these roentgenological findings may be absent in a special case. Furthermore, it must be stated that Ductus Botalli persistens is often combined with other anomalies, especially of the larger vessels (the subclavian artery) or anomalies in the heart (septal defect etc.).

From the above it will appear that the roentgenological diagnosis of Ductus Botalli persistens is both limited and difficult. One may presume that the roentgenological examination is a solid support and of great value to the clinical diagnosis.

It is necessary to mention that the »machine murmur» is the important pathognomonic sign.

It would be desirable from the roentgenological point of view to be able to demonstrate the shadow of Ductus Botalli persistens directly on the film.

JØNSSON has demonstrated very nice direct roentgenograms of the persistent ductus Botalli after injection of contrast through a ureter catheter direct in sinus Valsalvae.

English and American literature points out that in Ductus Botalli persistens there is often obscurity in the upper part of the »aortic window» *i. e.* under the concavity of the aortic arch. It is also mentioned that calcifications are observed both where the Ductus Botalli persistens leaves the aorta as well as where it joins the pulmonary artery.

Calcifications in the Ductus Botalli persistens are rarely described roentgenologically. Postmortally it has been described previously.

In September this year (1947) the Medical Department B of the University Hospital of Oslo, referred to the Roentgenological Department a patient who apparently had a quite distinct and complete calcified Ductus Botalli persistens.

The roentgenological findings will be demonstrated briefly.

Usual survey picture (Fig. I) shows a linear, downwards convex calcification projected on the lower part of the wall of the aortic arch. It has a somewhat unusual localisation to be a mere aortic calcification, as these generally are situated upwards and laterally. They may, of course, extend downwards to the base of the arch. Exclusively downward localisations, however, are more rare.

Planigraphy (Fig. IV) in various positions (lateral and frontal) gives quite a nice picture of the calcification. In the frontal planigram the calcification proves to be spherical. The lateral planigram shows a linear calcification with double conture extending downwards from the concavity of the arch and frontally towards the pulmonary artery.

The patient was 60 years old and could not, therefore, be operated on. The demonstrated calcification — one may gather — was a contra-indication against operation.

Fig. I.

Fig. II.

Fig. III.

Fig. IV.

Fig. I. Shows a calcification localisated in the aortic arch region.
Fig. II. Is a picture of the same calcification from the left. It is double contured and has the localisation of Ductus Botalli between the concavity of the aortic arch and the pulmonary artery. The aortic window is obscured.
Fig. III. Shows the calcificated Ductus Botalli in the first oblique position.
Fig. IV. A planigraphic film of the calcified Ductus Botalli.

Consequently operative verification of the diagnosis was impossible. The Medical Department B stated, however, that clinically the diagnosis undoubtedly was that of Ductus Botalli persistens.

The American Journal of Roentgenology, December 1947, describes a 37-year-old patient who was found postmortally to have a calcification of the Ductus Botalli persistens. The frontal roentgen picture of the heart of this patient demonstrated a calcification with similar localisation and appearance as in our patient. Our diagnosis was made as a consequence of these facts.

SUMMARY

The author demonstrates a direct picture of a completely calcified Ductus Botalli persistens. It is important to pay attention to the localisation and the form of the »aortic calcification». Roentgenologically demonstrated calcification in Ductus Botalli persistens is of some importance as a contraindication against operation.

ZUSAMMENFASSUNG

Verf. legt ein Direktbild eines vollständig verkalkten Ductus Botalli persistens vor. Es ist wichtig, die Lokalisation und Form der »Aortenverkalkung» zu beachten. Röntgenologisch nachgewiesene Verkalkung in einem Ductus Botalli persistens ist als Kontraindikation gegen Operation von gewisser Bedeutung.

RÉSUMÉ

L'auteur présente l'image, obtenue directement, d'un conduit persistant de Botal qui était complètement calcifié. Il importe d'accorder son attention à la localisation et à la forme de la »calcification aortique». La calcification, démontrée roentgenologiquement, d'un conduit persistant de Botal revêt une certaine importance en tant que contreindication à l'opération.

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FROM THE UNIVERSITY ODONTOLOGICAL LABORATORY, HELSINGFORS, FINLAND.

A NEW TOMOGRAPHICAL METHOD FOR RADIOGRAPHING CURVED OUTER SURFACES[1]

by

Yrjö V. Paatero

The present tomographic methods are applicable to — and perhaps also intended to be used mainly for — radiographing an imagined fixed area in a plane through the object intended for picturing. This plane can either pass through the object itself or touch its outer surface as a tangent.

As known, the tomographic radiography is based on the movement in given direction that is taking place between the roentgen tube and the object to be pictured. In the practice this is being arranged so that the tube is moving during the exposure either as a circular arch (GROSSMANN etc.), or along a linear track against the plane of the film (OLSSON). The latter method is especially suitable for radiographing plane outer surfaces.

The undersigned has outlined a new tomographic method, which is suitable for radiographing of curved outer surfaces. As the appliances required for the method — in fact very simple in construction — have so far not been placed at my disposal, I am in this connection only able to give a preliminary explanation of my method and of the results of my achievements, hoping after some time to be able to revert to this matter.

My research and experiments have especially been made to discover the suitability of my method in radiographing of the cranium in one plane, to form a so called »cranial chart», very near the same way as plane maps are produced from the globe. Also in here we can simultaneously see all the oceans and lands, even those situated on the different sides of the globe. Theoretically taken, the radiographing of a cranium in this way seemed possible to me, and experiments have proved that the theory also in practice is adaptable.

[1] Read at the Meeting of the Northern Association for Medical Radiology, Stockholm, June 10—12, 1949; submitted for publication, June 20, 1949.

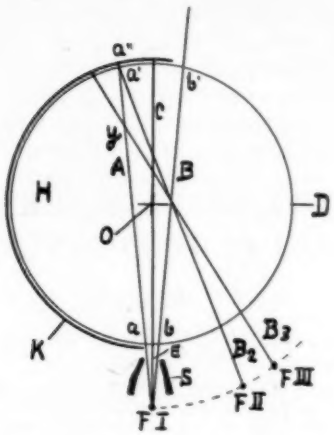

Fig. 1. Graphic presentation of tomographic radiographing of curved outer surfaces. A more detailed explanation in the text.

This method of mine is based on — same as all other tomographical methods — the even motion existing between the roentgen tube and the object to be pictured. And the movement is a rotary motion where the rotary axle passes vertically through the centre of the object.

The theory of my method is being illustrated by Fig. 1. In this the object (H) to be pictured is assumed to be cylindrical and this is to be examined in the illustration in a horizontal sectional plane, where the focus (F) is situated. The roentgen rays are naturally diverging after leaving the focus, and the size of the diverging angle depends on the width of the vertical slit, through which the rays are passing, as well as on the mutual distance between the aforesaid slit (E) and the focus. In order to be able to make the sharpest possible projection on the film only from that exterior surface of the object, which is situated near the film, so that the opposite side of the object (cranium) would not mix or disturbe the image to any considerable extent, just the divergence of rays is of some importance. Moreover it is important, that the focus is placed as near as possible to the object, as it is possible in this way also to obtain the necessary vertical divergency. This is of importance, because a cranium is a kind of combination of a cylinder and a ball. In the appliance of the method in the practice, we must endeavour to reach that theoretic ideal of cases, according to which the focus of the roentgen tube would be situated inside and in the centre of the cranium, projecting its rays from there in all directions on the periphery and on the ball-like film encircling the cranium.

In the illustration there are drawn three rays with focus as starting point. The ray passing through the rotary axis is a so called central ray (C). A and B are two of the outmost rays projected through the vertical

lit (E). These last mentioned rays are first cutting the periphery of the bject at points a and b and thereafter, when passing through the object anew, cutting the periphery at points a′ and b′, after which they re thrown on the film (K). As a result of the divergence in the rays he arc of the circle will be a′ b′ > ab, and thus that portion of the outer urface of the object, through which the cluster of rays is first passing, will be projected »unfolded» and thus taken on the film with reduced sharpness. On the other hand, the portion of the outer surface on the film side is being projected fairly sharp, under condition that the film is kept very close to the object. In taking pictures after this method in my practice, mainly of the face side of the cranium, the rays are thus first penetrating the back of the skull. And as the bone in that part of the cranium is fairly homogeneous, it acts only as a kind of screen without leaving any disturbing obscurities on the picture obtained of the front part of the cranium.

The divergence in the rays is having a further advantage, viz., that the points situated on the outer surface of the object on the film side or very close to it, as shown in Fig. 1 at point a′, are being projected on the film practically in the same place (a″), though the rays passing through them would to a certain extent vary in their direction. If we, for instance, study the illustration at point a′, where ray A and circumference D are cutting another, the focus attaining position I. In assuming, that the object is rotating around its axis (O) (or that the tube is having a corresponding motion) so that the focus comes to position II, in which the primary ray B (now B 2) will pass through point a′. The image of point a′ on the film projected by ray B 2 will appear practically in the same place as the image (a″) projected by ray A, under condition that the film is fairly close to the object. On the other hand, an other point (y), situated at some distance from the periphery towards the centre, is being projected on the film by the corresponding rays at a considerable distance from another. The object has to rotate about 180 degrees.

I think, that it by the aid of the above study will be easily understood, that my new method will make it possible to obtain fairly sharp pictures of a cranium, and especially pictures that are unfolded and form one plane.

The illustration 2 shows how I have thought the radiography to be carried out in practice. In front of the cranium (when taking a picture of the front side) is a cassette (K) into which the film is placed in the usual way between the usual intensifying screens. This cassette has to be of about a semi-cylindric form. To follow the shape of the head it can even be bent to a parabolical form, in order to be able to bring the film as near as possible to the object. The focus (F) is now to be brought as near the head as possible. The patient is sitting on a chair, especially

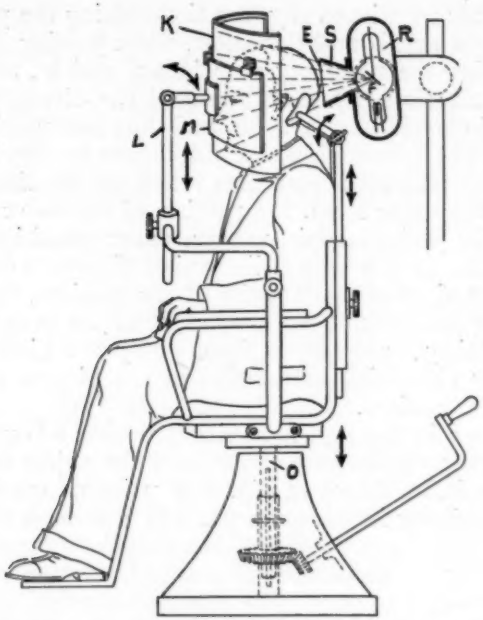

Fig. 2. Schematic picture of the apparatus which makes possible to radiograph half of the cranium spread like a plane. R = roentgen tube. F = focus. S = ray director in which a vertical slit (E). K = semi-cylindrical or parabolic cassette. O = rotary axis of the chair. L = forehead support where is the cassette holder (M). The chair is moved by hand or electric motor.

constructed to rotate 180 degrees and thus, that the assumed extension on the rotary axle (O) will pass through the centre of the head in the median plane. The vertical height where the focus is, is to be set to correspond with every case. The base of the skull usually leaves in the picture light, veil-like stripes (Fig. 3), the situation of which in the image depends on the place of the focus.

The roentgen apparatus (R) has a ray director (S), the utmost end of which having a vertical slit (E) for producing of a cluster of rays of a suitable form. It appears to me, that the width of the slit can be made to be about 2—4 mm, when the distance between the focus and the slit is about 20 cm. The height of the slit has to be so large that the vertical divergence in the rays is sufficient for producing an image comprising the whole height of the skull. When carrying out my experiments I have used 24 × 30 cm films, which size has proved sufficient for semi-

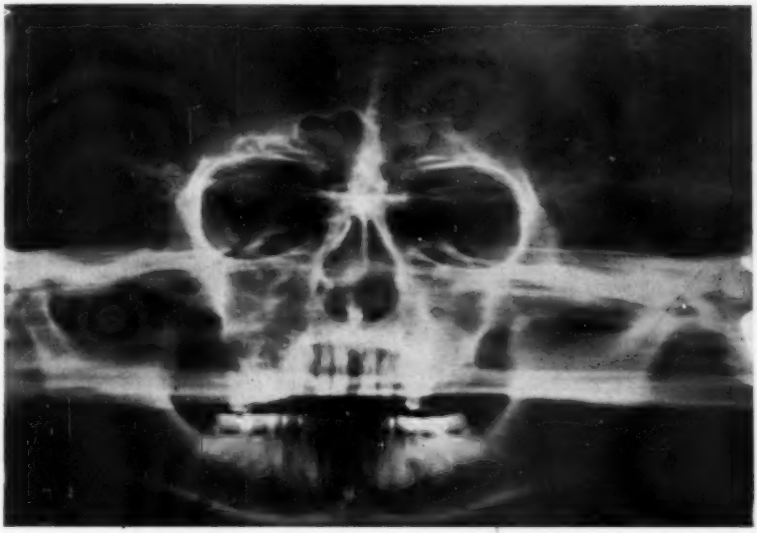

Fig. 3. Semi-cranial roentgenogram (»cranial chart») taken in the way shown in Fig. 2.

cranial images (Fig. 3). The roentgenograms taken in this way are in my idea very suitable for ascertaining a fracture.

My method can be also applied to other practical uses than those I have tried to explain here above, in my opinion for instance in a way illustrated by Fig. 4 and 5 schematically. Fig. 4 is showing the apparatus from above and Fig. 5 from the side. The patient is seated on a specially constructed rotary chair. The cog-wheel (A), while rotating, is carrying the cassette holder (B) in a linear and horizontal direction, as indicated by the arrow. The cassette holder is also provided with cogs that are gripping those on the cog-wheel (A). The cassette (K) can be made somewhat curved, in order to better correspond with the form of the head. The head (H) is kept firm during its movement with the chair and the thereto secured cog-wheel (A) and simultaneously is the cassette holder carried forward, so that a new area on the film always will receive the rays arriving through the head. To prevent scattering, a stationary apron (G) can be mounted between the cassette and the object to be radiographed. It can be made, for instance, of lead and provided with a vertical slit corresponding with the cluster of rays, through which slit only the rays are permitted to pass and to be projected on the film held in the cassette. By the use of these appliances it would be possible to radio-

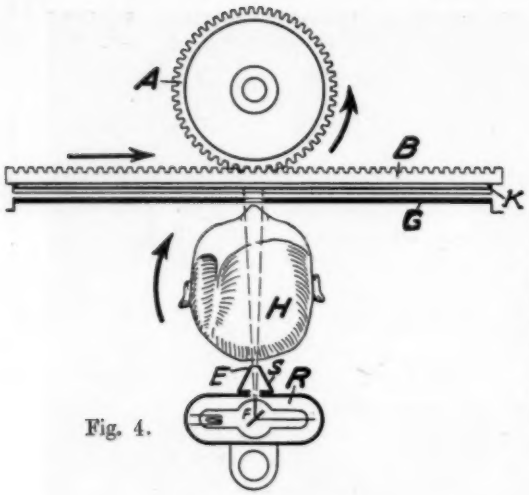

Fig. 4.

Fig. 4 and Fig. 5.
Schematic picture of the apparatus which makes possible to radiograph the whole cranium spread like a plane (»cranial chart»). A = cog wheel which carries the cassette holder (B) in which a curved cassette (K). G = lead apron to prevent the scattered radiation. R = roentgen tube. F = focus. S = ray director. I = neck support (of translucentic material).

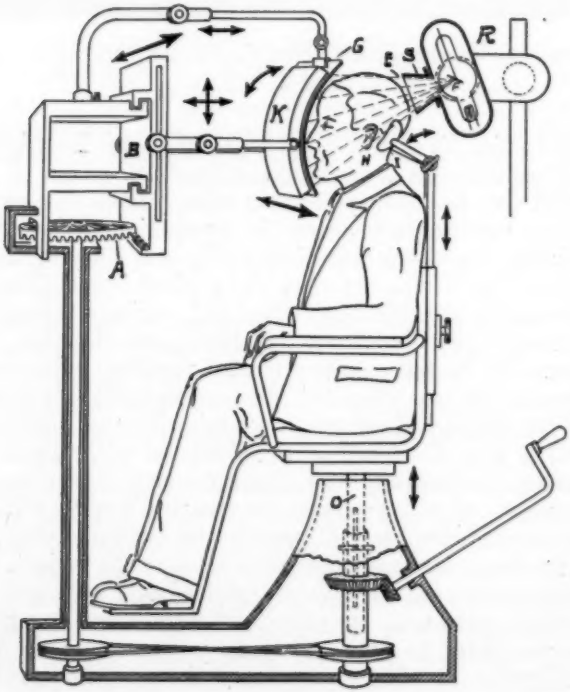

Fig. 5.

graph the whole cranium »unfolded» in one plane only. It is, however, very important that the focus is adjusted sufficiently high, so that the cluster of rays is penetrating the forehead above the orbit at the moment the face side is being turned to the roentgen tube, in order that the more dense bone construction of the face part would not to any greater extent cause obscurities on that part of the image that has been projected on the film from the rear side of the skull.

The reader can easily observe, that both of my methods are having their own advantages and disadvantages. For my own part I would at this moment place the first explained method, owing to its great simplicity, foremost. This because a semi-cranial radiography in most of the cases is sufficient and especially for the face side, of which images mostly are required.

Besides cranial radiography, my method could perhaps be applicable in some other cases, where a roentgenogram is required of expressly an arch-shaped outer surface or of a layer near it. It would perhaps be necessary to make experiments, in order to find out its suitability in thorax-picturing, amongst others, to determine the situation of caverna.

SUMMARY

The author has outlined a new tomographic method, which can be applied to the radiography of curved outer surfaces. The so far undertaken experiments according to this method are limited only to cranial radiography, for which purpose it has also proved to be suitable. By the aid of the method a roentgenogram of the cranium can be produced unfolded in one plane, so that the areas on different sides of the cranium appear in the picture side by side. From this kind of »cranial chart» it is easy to observe the eventual fractures already by the aid of only one picture. The picture is taken by means of a rotary chair, either by using a semi-cylindric film cassette secured to the head or by using a linearly moving film cassette. In each of the cases a narrow, somewhat divergent, cluster of rays is being projected through the head on the film cassette on the opposite side.

ZUSAMMENFASSUNG

Der Verfasser hat eine neue tomographische Methode entworfen, welche für Röntgenographierung bogenförmiger Aussenfläche geeignet ist. Mit dieser Methode hat man vorläufig nur Versuche für Röntgenographierung des Schädels gemacht, für welchen Zweck sie sich geeignet erwiesen hat. Durch diese Methode kann der Schädel röntgenographiert werden, als ob er auf einem Plan ausgebreitet wäre, so dass die an verschiedenen Seiten des Schädels vorhandenen Stellen auf dem Bilde nebeneinander sind. Mittels einer dergleichen »Schädelkarte» ist es leicht, eventuelle Frakturen schon durch ein einziges Bild zu beobachten. Die Röntgenographierung erfolgt auf einem rotierenden Stuhle entweder durch Anwendung einer halbzylinderförmigen am Kopf befestigten Kassette oder durch Anwendung einer geradlinig beweglichen Kassette. In beiden Fällen wird eine schmale, etwas divergierende Strahlenbündel durch den Kopf an die auf der anderen Seite desselben befindliche Kassette gerichtet.

RÉSUMÉ

L'auteur a projeté une méthode tomographique nouvelle convenant à la radiographie des surfaces extérieures arquées. Jusqu'ici la méthode n'a été expérimentée que pour la radiographie du crâne où elle s'est montrée d'une grande utilité. A l'aide d'elle on peut radiographier le crâne comme si on l'avait étendu sur un même plan de manière que les parties se trouvant de différents côtés du crâne sont sur la roentgenographie côte à côte. Dans une telle »carte crânienne» il est facile d'observer des fractures éventuelles déjà après une seule roentgenographie. On fait la roentgenographie à l'aide d'une chaise tournante et en employant, ou une cassette demi-cylindrique fixable à la tête, ou une cassette qui est en mouvement rectiligne. Dans les deux cas on dirige une gerbe de rayons étroite, peu divergente, à travers la tête vers la cassette qui est sur l'autre côté d'elle.

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THE FRONTAL SINUSES IN BRONCHIECTASIS[1]

A study on the morphological basis of lung disease

by

Johan Torgersen

In a previous paper the author has dealt with the frequent occurrence of bronchiectasis in individuals showing situs inversus. Another paper deals with the genic factors in the asymmetry of the viscera. The most reasonable interpretation of the data was that the asymmetry of the viscera depends on a complex of genes which act as modifiers concerning the genes influencing the development of the particular organs. According to this interpretation the combination of situs inversus and bronchiectasis is due to genes influencing the development of the lungs and showing incomplete dominance, the chance of manifestation depending on the homozygosity concerning the modifiers in asymmetry.

These problems are not of theoretical interest only. Bronchiectasis is a rather common disease and it is not irrelevant what part is played by heredity and what part by environment in the particular case. The environmental factors may be prenatal or postnatal. The disease may be due to prominently exogenous causes as vitamin A. deficiency of the mother or a foreign body in the bronchi. Between the extremes are the cases showing a varying influence of heredity and environment.

It is a common opinion among physicians that congenital bronchiectasis is extremely rare. However, this problem has been very much discussed and the disagreement between the authors is obviously due to the fact that they have based their opinion on selected cases. An internist like BRAUER (cit. DIEHL) is inclined to stress the exogenous factors. He is impressed by the frequent occurrence of pulmonary infections in the early childhood of these patients. SAUERBRUCH (cit. DIEHL) who knows a number of cases from the point of view of the surgeon, is impressed by

[1] Submitted for publication, June 28, 1949.

the frequent occurrence of a normal pleura and the rare occurrence of signs of infections in the lobes removed at the operation. Probably SAUERBRUCH has selected cases which in the roentgen-rays did not show pleural adhesions which may be a complicating factor during the surgical intervention. The statistically-minded physician is not convinced by the reasoning that bronchiectasis frequently is due to an infection of the lung in childhood particularly if it is complicated by bronchostenosis and atelectasis. Such affections are so extremely common in childhood that the real problem is why some children get bronchiectasis and others not, after the recovery from the infectious disease. As far as I know there is no study available proving statistically the rôle of the infectious diseases in bronchiectasis. It has eventually to be proved that bronchiectasis is more common in children having had infections of the lungs than in other children. This will probably prove to be no easy task. Casuistic observations are rather valueless. For the same reasons the time of the onset of the symptoms is of a limited value, evaluating the relative influence of endogenous and exogenous factors. Early onset of the symptoms without any obvious etiologic factor may arouse suspicion that the disease is congenital. Of course the time of the onset of the symptoms does not say anything as to the relative importance of environment and heredity.

The physician may get an impression of the importance of these two factors on the one hand by asking for similar symptoms in the family, on the other hand by applicating his knowledge in physiology and morphology on the particular case. A sound judgement of the physician on this point is important in evaluating the operability. The effect of the lobectomy depends on the risk of bronchiectasis in other lobes. They may be present from birth or the individual may have a particular predisposition for developing bronchiectasis.

The present study is based on a comparison between cases which may be regarded as congenital and cases which are mixed with regard to etiology. In 50 cases of bronchiectasis showing situs inversus the roentgen findings in the lungs were either small or negative. In no case were found signs of pleural affections or of primary affections of the lungs.

In 30 non-selected cases of bronchiectasis in individuals showing the normal situs the roentgen picture showed severe findings in 10 of the cases. Another third of the cases were elderly people also showing signs of a primary disease of the lungs. The last third showed smaller findings in the roentgen picture. Already a comparison between the findings in the lungs in situs inversus and in the normal situs demonstrates that in a non-selected material of bronchiectasis exogenous factors are prevalent.

KARTHAGENER and ULRICH have shown that the frontal sinuses are small in bronchiectasis.

Table I

The size of the frontal sinuses in 20 cases of uncomplicated situs inversus, in 20 cases of situs inversus showing bronchiectasis, in 30 cases of bronchiectasis in the normal situs and in 86 cases of bronchiectasis in the study of KARTHAGENER.

	Uncompl. Sit. inv.	Bronchiect. in sit. inv.	Bronchiect. in the norm. sit.	Sum total showing bronchiect.	%	Figures of Karthagener. %
Absent	1	5	3	8	16	20
Small	4	6	9	15	30	35
Medium	11	8	9	17	34	41
Large	4	1	9	10	2	4

An χ^2 analysis of the first two groups gives $\chi^2 = 9.6$ and $p = 0.01$ by two degrees of freedom. An analysis of the difference between the first and the third group and between the second and the third group gives in both cases $\chi^2 = 1.88$ and $p = 0.50 - 0.30$ by two degrees of freedom.

In the table I have compared the size of the frontal sinuses in uncomplicated situs inversus, in bronchiectasis in situs inversus, and in bronchiectasis in the normal situs. The last column gives the figures of KARTHAGENER. The extension of the frontal sinuses in the squama is taken as a sign of the pneumatization of the frontal bone. No frontal sinuses in the table means no sinuses in the squama. The deviations from the data of KARTHAGENER, which also include a number of cases of situs inversus, are the same in all groups, a fact indicating that the observations are rather conform, the estimation of the size being different only.

The χ^2 analysis shows a significant difference between the size of the frontal sinuses in the cases of situs inversus showing, and those not showing bronchiectasis respectively. The difference between the other groups is not significant. However, the individuals showing bronchiectasis and the normal situs have an intermediate position between the uncomplicated cases of situs inversus and the cases of situs inversus showing bronchiectasis. The sinuses are thus probably smaller in the group showing congenital bronchiectasis than in the group which is mixed concerning etiology. If all the cases of bronchiectasis are taken together the frontal sinuses are absent in 8 cases, in 16 per cent $\pm$ 5.2. In 400 skull roentgenograms the frontal sinuses were absent in 5 per cent $\pm$ 1. The difference may be regarded as significant, an observation confirming the observations of KARTHAGENER. It may be concluded that the frontal sinuses are small in bronchiectasis due to the small sinuses in the congenital cases. The small sinuses in the congenital cases may be a clue to the evalutation of the relative importance of hereditary factors in

the particular case. If a patient shows bronchiectasis and at the same time very small findings in the lungs and small frontal sinuses the probability is great that we have to deal with a case of congenital and also hereditary bronchiectasis.

All ten of the twenty individuals showing bronchiectasis and situs inversus and in whom the frontal sinuses had been examined, had symptoms of severe sinusitis, 5 of them having been operated on for nasal polyps. These symptoms were found in all the five individuals showing absence of the frontal sinuses. The rather frequent occurrence of nasal polyps in these individuals is known through the studies of KARTHAGENER and OLSEN. Ten of the individuals showing bronchiectasis and the normal situs also had sinusitis, one of them showing nasal polyps. According to observations in patients showing bronchiectasis the combination of bronchiectasis and sinusitis may be due to a secondary affection of the sinuses, or the lung disease may be secondary in relation to the sinus trouble. The problem naturally arises whether the defective pneumatization is due to the swelling of the nasal mucosa in childhood. There are no conclusive observations or experiments regarding this problem. However, sinus trouble in childhood is so common that defective pneumatization might be expected to be very common if there was a simple causative relationship between sinusitis and pneumatization.

The observations by SCHWARZ in twins suggest that the size of the sinuses partly depends on hereditary factors. In a familial case of situs inversus I found a remarkable conformity of the frontal sinuses in three sisters, all of them showing bronchiectasis, and two of them situs inversus (Figs. 1, 2 and 3). The father showed bronchiectasis, the mother, two brothers and a sister nasal symptoms. Two brothers had no symptoms from the lungs or the nose. The frontal sinuses in the other members of the family were of average size. One of the sisters showing bronchiectasis also showed a metopic suture.

In a study of the metopic suture I was able to confirm the observations of ROCHLIN and RUBASCHEWA, that the frontal sinuses are small in individuals showing the metopic suture. It is known that the frontal sinuses are small in ozaena, a disease which also may affect the upper respiratory tract. The observations available, among others by KNORRE, are good evidence that ozaena may be hereditary in connexion with a defective development of the ectoderm. The metopic suture occurred in 3 of the 40 skulls examined in situs inversus, all these belonged to the 14 families showing signs of the lung/nose syndrome. It was found in a girl whose mother and maternal grandfather showed severe symptoms from the nose. The metopic suture behaved as an hereditary anomaly in this family. The members showing metopism had the infantile face with the broad forehead, the broad low root of the nose and the small

Fig. 1.

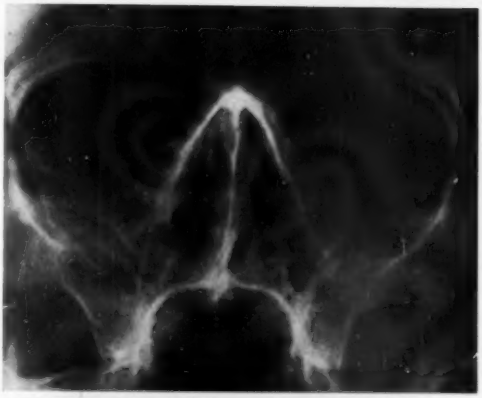

Fig. 2.

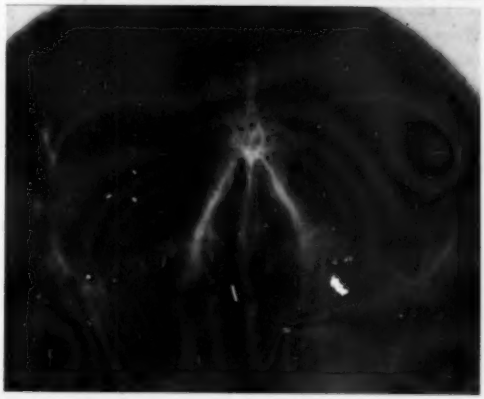

Fig. 3.

frontal sinuses, so characteristic both in ozaena and in the metopic skull.

These observations are rather good evidence that the development of the upper respiratory tract, including the sinuses and even the shape of the upper face, and of the lower respiratory tract, depend on the integrative action of a complex of genes.

The puzzling combination with situs inversus depends on the integration of this genic complex and the modifiers in the asymmetry of the viscera. During development the inversion may come into existence by means of the abnormal differential growth of the layers of the lung. The torsion of the viscera may depend on the same laws of growth as torsion in biology generally as seen in the accretionary growth of the shell of snails and of the horn of cattle. The torsion depend upon the relative growth of the layers and the asymmetry of the points of the slowest growth. Abnormal asymmetry in the relative growth of the lungs may cause inversion of the heart due to the relationship to the 6th aortic arch and of the abdominal viscera, due to the relationship of the lung bud to the foregut.

The abnormal development resulting in bronchiectasis and the small frontal sinuses may affect other parts of the body. In situs inversus the variability of the spine is increased showing the relationship between symmetry and metamerism. In the same way according to KERLEY abnormalities of the ribs are rather common in bronchiectasis. In the present study three of the individuals showing situs inversus and bronchiectasis showed signs of hypogenitalism. A parallel observation is cited by DIEHL. Two of them were brothers and in both families the parents were second cousins. The observations show the general character of the effects of the genic factors in bronchiectasis expressing themselves in the constitution of the individual.

The relationship of the development of the entodermal lung buds to bronchiectasis and the asymmetry of the viscera, is expressed in the localization of bronchiectasis. As known the anomaly prefers the lobes showing asymmetry concerning the relationship between bronchi and vessels. Pneumonia in childhood shows the same preference for the right upper lobe and the lower left. Tuberculosis on the other hand shows no relationship to the asymmetry of the lungs. In most cases tuberculosis originates in the terminal bronchioli or in the acini, the bronchial wall itself being rarely affected primarily by tuberculosis. The risk of infection with tuberculosis depends on the passage of the air to the acini. From the fact that the pigmentation of the surface of the lungs is less marked in cases of congenital bronchiectasis it may be concluded that the chance that the bacilli shall reach the acinus is smaller in bronchiectasis than in the normal lung. The delayed resorption of the lipiodol in

bronchiectasis demonstrates the low resorptive power of the lung in bronchiectasis, another factor which makes it less probable that the bacilli are going to penetrate into the connective tissue. There are few observations available concerning the relationship between bronchiectasis and tuberculosis. KARTHAGENER reports two cases of bronchiectasis in one lung, tuberculosis in the other and one case in which tuberculosis occurred in the lung showing congenital bronchiectasis.

Discussing bronchiectasis and the relative importance of endogenous and exogenous factors in the etiology of the disease one has to keep in mind that bronchiectasis is both a clinical and an anatomical conception. In this paper I have only dealt with the clinical conception because we cannot diagnose bronchiectasis which give no symptoms. Nor do we know much about the variability in the microscopical structure of the lung. For this reason one has to be rather reserved in drawing conclusions concerning the etiology from casuistic observations. We really never know the morphology of the lung of the child in the particular case. The only way so far is to study the hereditary background and the general morphology of the individual. The susceptibility to lung diseases has a morphological as well as a serological aspect. Reasoning based on the latter aspect has been in vogue for years. It may come out to be wise not to forget the morphological aspect.

SUMMARY

The frontal sinuses are small in individuals showing bronchiectasis. They are smaller in a group showing congenital bronchiectasis than in a non-selected group. To judge from the difference as to the size of the frontal sinuses in the two groups congenital bronchiectasis is a rare disease. The roentgen findings in the lungs are small in the congenital cases. An examination of the lungs and the frontal sinuses may indicate the relative rôle of hereditary and environmental factors.

The most reasonable interpretation of the observations may be that the development of the upper and lower respiratory tract depends on the integrative action of a complex of genes. The manifestation of these genes depends on modifiers influencing the asymmetry of the viscera.

From the morphological point of view there is possibly a negative correlation between congenital bronchiectasis and tuberculosis.

ZUSAMMENFASSUNG

Die Stirnhöhlen sind bei Menschen mit Bronchiektasen klein. In einer angeborene Bronchiektasen aufweisenden Gruppe sind sie kleiner als in einer nicht-ausgewählten. Nach dem Grössenunterschiede der Frontalsinusse in den beiden Gruppen zu urteilen, stellen angeborene Bronchiektasen einen seltenen Krankheitszustand dar. Die Röntgenbefunde in den Lungen sind bei den angeborenen Fällen gering. Untersuchung der Lungen und der Stirnhöhlen kann für die relative Rolle der Vererbung und der Umweltfaktoren Anhaltspunkte geben.

Die wahrscheinlichste Deutung der Beobachtungen ist vielleicht, dass die Entwicklung der oberen und der unteren Luftwege von der massgebenden Wirkung eines Genenkomplexes abhängt. Die Manifestation dieser Genen hängt von Faktoren ab, die die Asymmetrie der Eingeweide beeinflussen.

Vom morphologischen Gesichtspunkte aus liegt vielleicht ein negativer Zusammenhang zwischen angeborenen Bronchiektasen und Tuberkulose vor.

RÉSUMÉ

Les sinus frontaux sont petits chez les individus atteints de bronchectasie. Ils sont plus petits dans un groupe présentant de la bronchectasie congénitale que dans un groupe non sélectionné. A en juger d'après la différence de grandeur des sinus frontaux dans ces deux groupes la bronchectasie congénitale est une affection rare. Les constatations roentgenologiques au niveau des poumons sont discrètes dans les cas congénitaux. Un examen des poumons et des sinus frontaux peut indiquer le rôle comparatif des facteurs héréditaires et des facteurs extrinsèques.

L'interprétation la plus logique de ces observations, c'est probablement de dire que le développement des voies respiratoires supérieures et inférieures dépend de l'action intégrante d'un complexe de gènes. La manifestation de ces gènes dépend de modificateurs influençant l'asymétrie des viscères.

Au point de vue morphologique il est possible qu'il existe une corrélation négative entre la bronchectasie congénitale et la tuberculose.

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PEPTIC ULCER OF THE OESOPHAGUS[1]

by

Gregers Thomsen

QUINCKE, in 1879, gave one of the first descriptions of peptic ulcer of the œsophagus. At the same time he reported the patho-anatomical changes which consisted in a localized loss of substance in the mucous membrane extending more or less into the submucosa and attended with inflammatory changes in the surrounding tissues. At times the ulceration encroached upon the underlying connective tissue or muscles. In other words, the resemblance to the changes seen in gastric or duodenal ulcer was striking. For years this lesion was regarded as a curiosity and thought to be extremely rare. In 1906 TILESTON added his own cases to those reported in the literature and arrived at only 44. In 1929 STEWART & HURST found only 1 case among 10,000 post-mortem examinations and collected 11 additional cases from the literature. In the same year a remarkable paper was published by CHEVALIER JACKSON who found no less than 88 cases among 4,000 œsophagoscopies. Of them 21 were active, whereas the remaining 67 had healed. He concluded that the disease was far more common than generally supposed and that patients complaining of pain on swallowing or exhibiting obscure dyspeptic symptoms should always be suspected of œsophageal ulcer. Since the appearance of CHEVALIER JACKSON's paper the reports of this condition have greatly increased. FRIEDENWALD, FELDMAN & ZINN have reported 13 cases and several authors have reported 1 case each. In Denmark MEULENGRACHT and HINDSE-NIELSEN have reported 1 each and NØRGAARD 2.

It is difficult to state the frequency with certainty. Extremely varying results have been found by analyses of post-mortem materials. As already stated, STEWART & HURST found only 1 among 10,000 post-mortem examinations. GRUBER, who found 6 among 2,400, stated that the incidence of œsophageal ulcer as compared with gastric or duodenal ulcer was 1 : 30. Finally, LYALL found 8 cases among merely 1,500 post-

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mortem examinations. These marked variations are not at all surprising, as the detection of the condition depends partly on the attention given to its existence, partly on the degree of post-mortem changes which are particularly apt to occur in the œsophageal mucosa and which may blur or completely obliterate the signs of the lesion.

In 1926 ÅKERLUND classified œsophageal hiatal hernias into 3 groups. The first group comprised hiatal hernias with a congenitally short œsophagus, the second para-œsophageal hiatal hernias, and the third hiatal hernias in which the herniated content is the cardia, the adjacent part of the stomach and the lower end of the œsophagus. Unlike the first group, the last one shows an œsophagus of normal length. According to ÅKERLUND the first group, also called short œsophagus, was the most uncommon one, but after the appearance of FINDLAY & KELLY's paper from 1931 the condition has become better known and numerous reports have been published of short œsophagus, *inter alia* from Denmark by H. CHRISTIANSEN in 1941 and by E. WAMBERG in 1947.

Gradually it was noticed that peptic ulcer of the œsophagus co-existed with short œsophagus with striking frequency. This combination was first described by HAROEN & GERLINGS in 1934, later by HURST, BRIGGS & DICK in 1939 and in the same year by FELDMAN. In 1942 DICK & HURST published 16 cases and in 1943 ALLISON, JOHNSTONE & ROYCE 10. Only 5 years later ALLISON was able to collect 74 cases. In the same year, 1948, OLSEN & HARRINGTON of the Mayo Clinic, studying 220 patients with short œsophagus, found œsophageal ulcer in 110 of 149 submitted to œsophagoscopy.

As stated above, peptic ulcer of the œsophagus can no longer be considered a rare lesion. This receives further support from a review of the diagnoses from the Radiological Department of the University Hospital in Copenhagen. Since 1936 this diagnosis has been made in 27 instances. Fifteen of the patients were males and 12 females, so there is no sex difference worth mentioning. This accords with recent findings, but previously it was thought that there was male predominance at a ratio of 3 : 1.

The age distribution was as follows:

0—5	6—10	11—20	21—30	31—40	41—50	51—60	61—70	71—80
8	3	2	1	2	4	2	4	1

The stated age is that when the diagnosis was made. It will be seen that there is an accumulation of cases in the youngest and oldest age groups. Ordinarily the disease is stated to be most common in the 3rd to 7th decades (FELDMAN). Among ALLISON's 74 cases 56 were older than 50. Several reports have, however, appeared of peptic ulcer of the œsophagus in children (NØRGAARD; ALLISON). As mentioned above peptic

ulcer of the œsophagus very often co-exists with short œsophagus. A classification of the material from this point of view reveals that this combination was found in 18 patients of whom 11 were under 10 years of age, whereas 7 were between 40 and 80. The 9 patients who had peptic ulcer of the œsophagus without short œsophagus ranged in age from 0 to 70, the two youngest being 15 and 16.

The symptoms of œsophageal ulcer co-existing with short œsophagus were mainly pain and difficulty in swallowing, vomiting or regurgitation, and hæmatemesis or melæna. The severity of the symptoms varies in children and adults.

In children the vomiting is an outstanding symptom. It may occur immediately after or during the meal, but in a few cases it was delayed for several hours after the meals. In the majority of cases the vomitus consisted of undigested particles of food, but it might also, especially when the vomiting occurred some time after meals, be composed partly of digested, acid food components. In addition, all the children had a history of hæmatemesis at some time or other, varying from minor blood streaks to profuse, repeated hæmatemeses necessitating blood transfusions. At times pain on swallowing or epigastric pain were outstanding symptoms when the children were in the horizontal position, and it was a characteristic feature that some of the children felt best sitting; one of them had even formed the habit of sleeping in a sitting posture. Only a few complained of pain on swallowing. A child of 6 exhibited complete stricture of the œsophagus treated with jejunostomy, but the patient died from anaphylactic shock 4 days later. In all instances the symptoms had been present right from birth or had set in during the first months of life. In 3 cases the vomiting had first been interpreted as a sign of pyloric stenosis. The intensity of the symptoms varies. During bad periods the children may be extremely debilitated, emaciated, and anæmic, and their development may be delayed, whereas in good periods their life may be fairly tolerable.

Below will be reported a few characteristic case histories:

I. A girl, born on Aug. 8, 1927. Ever since she was a baby she had been apt to vomit in connection with the meals, and a few times the vomitus had been blood-stained. Her condition fluctuated between good and bad periods. From 1929 to 1942 she had been hospitalized 8 times. She had repeatedly been treated with bougie and duodenal tube. Each treatment had resulted in brief improvement. From the age of 6 she began to complain of pain behind the sternum and she suffered periodically from pain on swallowing attended with weight loss.

In 1930 roentgen examination of the œsophagus (Fig. I a) showed marked dilatation of the upper end. On a level with the 9th thoracic vertebra it tapered into a quite short and thin canal which opened into the cardiac orifice which was situated above the diaphragm. The remaining part of the stomach was normal. This was a typical case of short œsophagus, but without signs of œsophageal ulcer. In 1936 (Fig. I b) the dilatation of

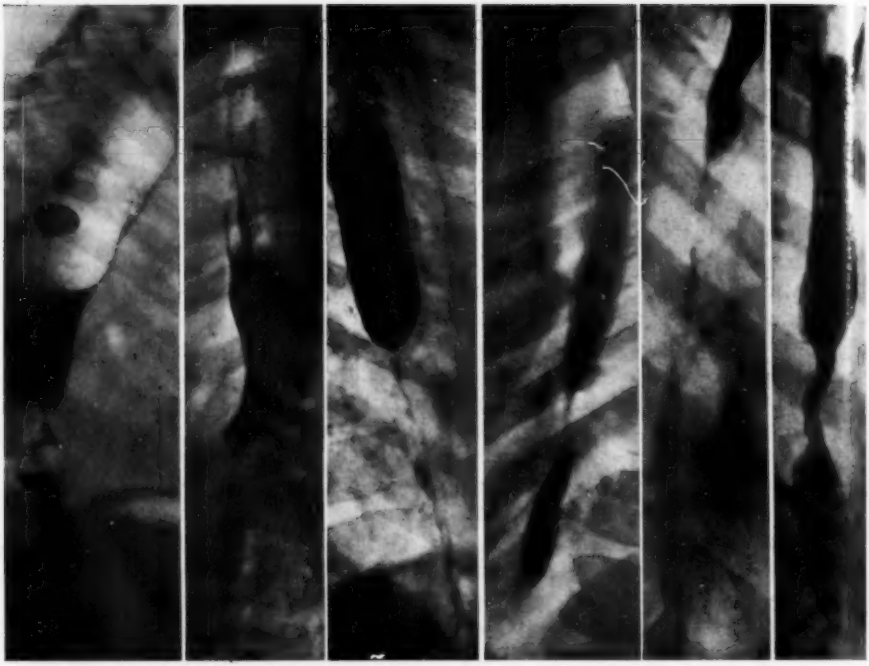

Fig. I a. I b. I c. I d. I e. I f.

the upper end of the œsophagus was found to be unchanged. The constricted segment was longer, and 1 cm below its commencement there was a patch of barium, as large as the head of a pin, no doubt indicating a niche. As on the earlier film the œsophagus was short and there were distinct signs of hiatal hernia. Now, we also had evidence of œsophageal ulcer. In 1937 (Fig. I c) the dilatation was less marked, but this time too the niche was demonstrable. In 1939 (Fig. I d) the dilatation had further decreased, the constricted segment measuring $1^1/_2$ cm. This time the niche could not be demonstrated. In 1941 (Fig. I e) the niche was again visible slightly below the middle of the constricted segment. Finally, in 1942 (Fig. I f), the constricted segment was again distinct, being 3 cm long with a lumen of $^1/_2$ cm. This time there were not signs of ulcer, but the mucous membrane revealed marked œsophagitis.

The patient has repeatedly been examined by œsophagoscopy, in 1936, 1939, and 1941. The first time the œsophagus was found to be dilated, and 27 cm. from the front teeth there was a stricture surrounded by a swollen and reddened mucosa. In addition, there was some hæmorrhage, and the finding was interpreted as ulcer. The second time only the stricture was seen, and the third time there was distinct reddening and membrane formation.

II. A girl, born July 29, 1942. Since the age of 3 weeks she had suffered from frequent vomiting of an explosive nature, occurring nearly always in connection with the meals, at times 2—3 hours after. The patient was hospitalized at the age of 3 months

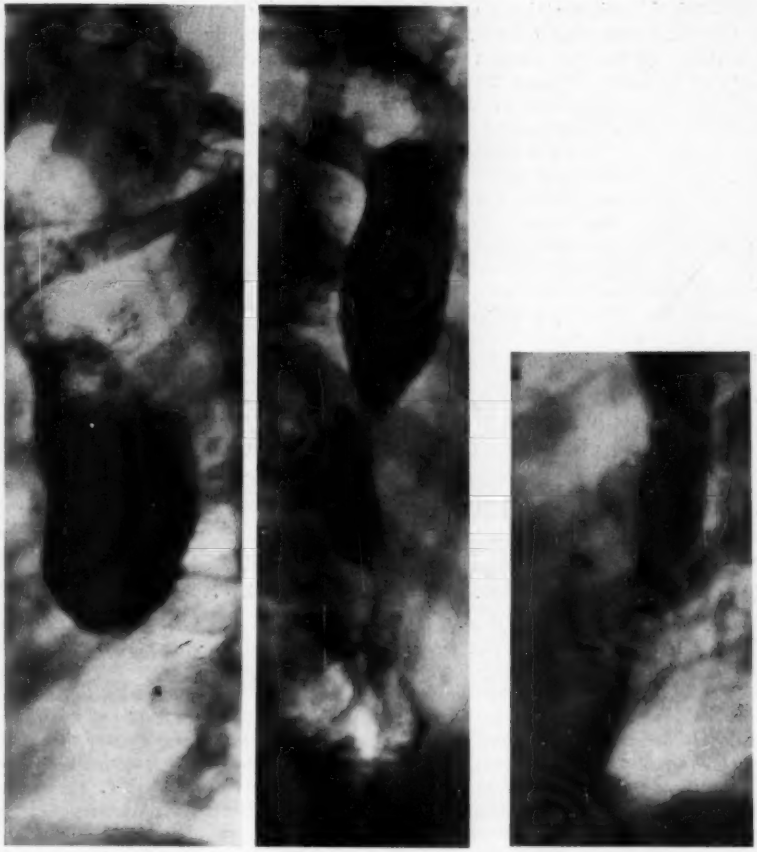

Fig. II a. II b. II c.

and a diagnosis of pylorospasm and avitaminosis K was made. During the stay in hospital the fæces were invariably blood-stained. At the age of 4 years she was re-admitted and was this time thought to be suffering from nervous emaciation. Her condition has fluctuated; there have been good and bad periods, her appetite has been good all the time, but after meals she got a feeling of pressure in the epigastric region, her respiration became heaving, she looked as if she were going to suffocate, and then she vomited. During the last 6 months her condition had deteriorated; she had lost weight and the vomitus had at times been blood-stained. In 1947 she was admitted to the University Hospital, Department of Child Psychiatry, whence she was transferred to the Children's Department.

Roentgen examination of the œsophagus and stomach (Fig. II a) showed marked dilatation of the upper end of the œsophagus, the lumen being $3^1/_2$ cm. On a level with

the 8th—9th thoracic vertebræ the barium was held up, and it was long before the œsophagus emptied. Screening showed that the barium suddenly passed into the stomach and it was found that the cardiac orifice as well as the adjacent part of the fundus were situated above the diaphragm. There were no signs of an ulcer crater. A diagnosis of short œsophagus was made and 17 days later the same findings (Fig. II b) were made. In the meantime dietetic management was instituted, and 14 days later she was again examined by roentgen. This time the dilatation proved to have subsided almost entirely. At the site where the barium had previously been held up there was a constricted segment of about 1 cm in length. About the middle of this constricted segment there was a niche (Fig. II c), about the size of a hemp-seed, and there was no doubt that in addition to the short œsophagus the patient was suffering from a peptic ulcer of the œsophagus.

Œsophagoscopy was performed in the Ear, Nose and Throat Department. The œsophagus was found to be dilated, but 21 cm from the front teeth there was a concentric constriction with only a very small opening which did not admit the œsophagoscope.

The adult patients suffering from short œsophagus and peptic œsophageal ulcer complained mostly of retrosternal pain, at times radiating into the back, when the food passed the œsophagus. This pain was most marked following ingestion of solid foods. In addition, they had difficulty in swallowing and a sensation that the food was being held up at the lower end of the œsophagus. Only a few reported regurgitations. None of the patients had a history of hæmatemesis. In three instances the fæces were searched for blood, with a positive result in two. Weight loss did not occur. The symptoms had lasted from 6 months to 10 years.

III. A male, aged 51, who for the last 10 years had been suffering from eructations and regurgitations of acid-tasting gastric contents. The symptoms were mainly present at night and only when he lay on his right side, disappearing when he turned over. For the last few years there had, in addition, been a feeling of pressure in the epigastric region immediately after meals. He had noticed that he felt best standing after meals. There was no history of melæna. In March 1948 the patient entered the Department of Thoracic Surgery. Roentgen examination of the œsophagus and stomach (Fig. III a) showed moderate dilatation of the œsophagus. On a level with the 9th thoracic vertebra it tapered and passed directly into the stomach, the cardiac orifice and adjacent part of the fundus being above the diaphragm. Several of the films (Fig. III b) showed a dense patch of barium on a level with the constricted area at the site where the œsophagus passed into the stomach. In other words, it was a case of short œsophagus as well as œsophageal ulcer.

On March 27, 1948 operation revealed a short œsophagus and a hiatal hernia of 6—7 cm. The hiatus admitted about 4 fingers. The diaphragm was sutured to the œsophagus and the phrenic nerve resected.

The 9 patients, all adults, with œsophageal ulcer, but no demonstrable signs of short œsophagus, had the same complaints as the adult patients who suffered from ulcer co-existing with short œsophagus. The duration of the disease ranged from 2 months to 15 years. Six suffered from pain on swallowing, localized at the top of the epigastric region or behind the sternum. Seven complained of difficulty in swallowing, and

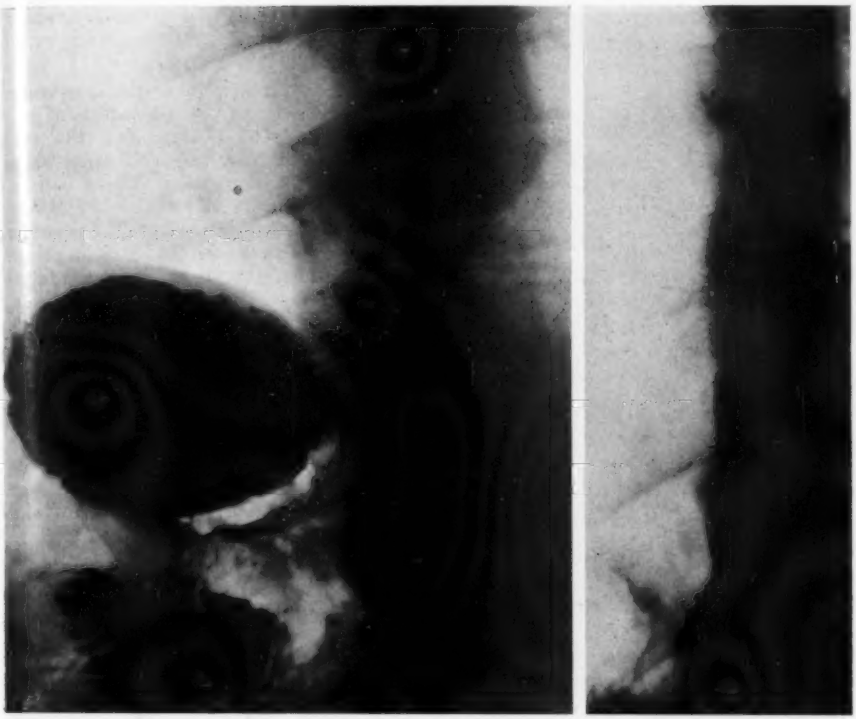

Fig. III a. III b.

5 of regurgitations of food remains or mucus. None had had hæmatemesis, but 3 had occult hæmorrhage.

No less than 4 also showed signs of gastric ulcer and had for some years had symptoms such as tardive pain, relief after taking of food, and copious, acid vomiting. In these cases the gastric symptoms had existed prior to the signs of the œsophageal lesion.

IV. A male, aged 60. During the last 15 years he had had symptoms typical of duodenal ulcer, and had received medical treatment in 1945. Some time after he began to have difficulty in swallowing, the food being held up at the lower end of the œsophagus, where it might remain for hours before it passed on or the patient vomited. Simultaneously there was a feeling of pressure behind the sternum. The difficulty in swallowing varied, being at times negligible and at other times so marked that nothing would pass. In 1946 gastrostomy was established. His condition deteriorated and was several times complicated by melæna and anæmia. In 1947 a tumour was suspected, but œsophagoscopy showed an œsophageal ulcer and a biopsy specimen revealed simple ulcer.

Fig. IV.

The patient was admitted to the University Hospital, Department of Thoracic Surgery, in November 1948.

Roentgen examination of the œsophagus (Fig. IV) showed marked dilatation of the œsophagus which 6—7 cm above the diaphragm tapered into a very thin canal which hardly allowed of the passage of the barium. It took half an hour to fill completely and then a patch of barium projected from the posterior aspect to the right. Nothing was to be gained from the films of the stomach, as the filling was too poor. It was without a doubt a case of peptic ulcer of the œsophagus. On November 9, 1948 transthoracic gastric and œsophageal resection and gastro-enterostomy were done. There was marked fibrous thickening of the lower end of the œsophagus which adhered to the surroundings, and the removed specimen showed an almost complete stenosis of the œsophagus. An ulcer was found above the cardiac orifice. In addition, the operation revealed a pyloric ulcer.

One patient had exhibited symptoms of cardiospasm 15 years previously and had been treated with dilatation by the method of Plummer. Now, roentgen examination showed only slight dilatation of the œsophagus which immediately above the diaphragm tapered into a narrow canal, 3 cm in length, and opened into a normal stomach. About the middle of the canal there was a niche, as large as a pea, doubtless a sign of peptic ulcer of the œsophagus.

The remaining 4 patients failed to exhibit any symptoms of present or past lesions of the œsophagus or stomach apart from the œsophageal ulcer. Neither were such lesions demonstrable by roentgen.

In one case 2 ulcers were found.

V. The patient was a girl, aged 16. The mechanism of swallowing had been completely normal until 3 months ago when she began to have difficulty in swallowing, to start with only when taking solid foods, but later also with fluids. There was no history of pain on swallowing, but there had been some vomiting of food remains. No hæmatemesis. In August 1947 the patient was admitted to the University Hospital, Ear, Nose and Throat Department.

On admission roentgen examination of the œsophagus and stomach (Fig. Va) showed moderate dilatation of the œsophagus. On a level with the 7th thoracic vertebra it be-

Fig. V a. V b. V c.

came constricted, continuing towards the stomach in the form of a narrow canal. The stomach was normal and there were no signs of hiatal hernia. No ulcer crater was demonstrable in the œsophagus. Renewed examination 2 months later (Fig. V b) showed more marked dilatation of the œsophagus. This time there was, in addition, a concentric constriction, 2 cm in length, opposite the 4th thoracic vertebra, and in the middle of this constriction there was a small niche. Below the constriction the dilatation continued as far as the 7th thoracic vertebra where another constriction was seen as previously, and this time a distinct niche was demonstrated. It was thus a case of two œsophageal ulcers. When reexamined in October 1948 (Fig. V c) the patient did not exhibit any signs of ulcer. Œsophagoscopy showed, 22 cm from the front teeth, a constriction. The wall grew stiff, preventing further progress of the œsophagoscope, but the opening was wide

enough to admit a little finger. A thin bronchoscope was passed, and 28 cm down there was a complete stenosis where some reddish tissue was visible. It was considered to represent an œsophageal ulcer. The patient was treated with bougies with a satisfactory effect.

The roentgen diagnosis is based on the characteristic niche in the œsophagus. It may, however, be extremely difficult to demonstrate, but in most cases the ulceration entails reaction in the surrounding tissue appearing on the film as a narrowing of the œsophageal lumen. Such narrowing strongly suggests an œsophageal ulcer. The niche is usually just above or a few centimetres above the cardia. Only in one case was it encountered at a higher site. In most cases the niche was rather small, ranging in size from that of a hemp-seed to a pea. In a few instances it was, however, larger, the largest one seen in our Department being $2 \times {}^{1}/_{2}$ cm. The niche was in most cases flat, being in only one case rather more than 1 cm deep. According to most authors the niche proper is rarely demonstrable. Thus, JOHNSTONE could demonstrate it in only 5 of the 74 patients who make up ALLISON's material. This is not quite in accordance with our experience, as we succeeded in demonstrating a niche in no less than 21 of 27 patients. It is, however, right to emphasize that a number of the patients were examined repeatedly and a few at several years' intervals before the diagnosis could be made.

As already mentioned, the ulceration is accompanied by a constriction, in acute cases due to oedema and inflammatory changes, which may vary from one examination to another. In most papers on peptic ulcer of the œsophagus this constriction is called a spasm. This is, however, misguiding, as it is not caused by contraction in the surrounding muscles and is not affected by anti-spasmodics. In those cases where the ulceration is of long standing, the narrowing is more marked and is constant on account of infiltrative, inflammatory and fibrous changes in the œsophageal wall, *i. e.* a stricture has resulted. A common feature of both kinds is the difficulty in getting the barium past the narrow site and the dilatation of the overlying part of the œsophagus. This dilatation may become extremely marked. In addition, the mucous membrane will usually exhibit œsophagitis. If the narrowing is due to inflammatory œdema, as in the acute cases, the overlying column of barium shows a rounded lower contour. Fluoroscopy shows that the contrast medium is held up for a long time, but after some time the œsophagus may empty rapidly and completely. As a rule the niche is not demonstrable at this time. If the examination is repeated, when the acute irritation has yielded to dietetic or other treatment, the barium will pass more easily, but the emptying will still be somewhat delayed. This affords better filling of the narrowed area, and in our experience, the niche will be distinct in the majority of cases. If the changes have resulted in a stricture, the

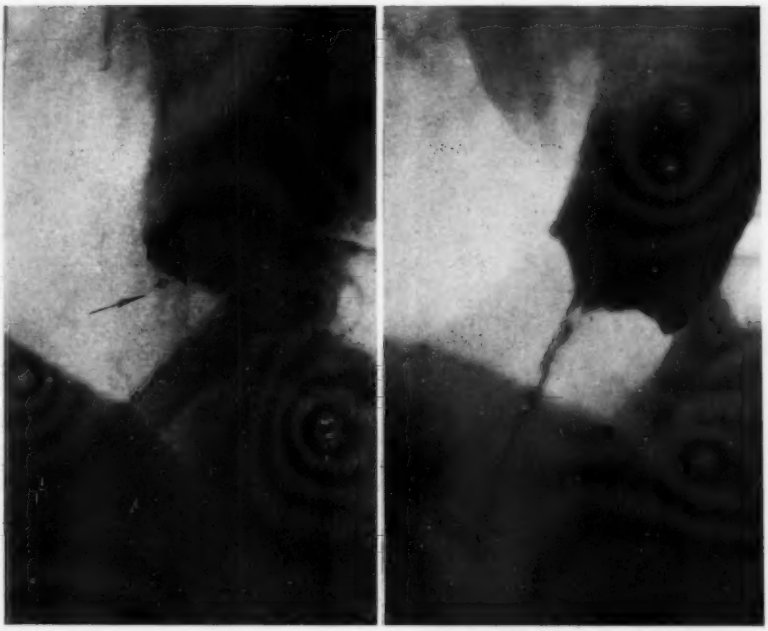

Fig. VI a. VI b.

overlying column of barium will taper more, but still show slightly convex edges. The retention is often more marked and the œsophagus empties but slowly. The stricture may be rather long, up to 5—6 cm. If the narrowed area fills with barium, the niche usually fills too.

It is easy to diagnose a short œsophagus and hiatal hernia in those cases where the hernia is large, but it may be difficult to point out less marked changes. In small children the œsophagus, as well as the entire alimentary tract, has a power of changing its volume to a great extent. During screening the barium is seen to pass through the œsophagus in the form of an oval bolus, whereas in adults it resembles a column. Even the lower end of the œsophagus and the cardiac orifice are capable of dilating perceptibly, and a film made at that moment may lead one to believe that it is a case of hiatal hernia filled with barium. Demonstration of gastric mucosa above the diaphragm is, however, decisive. The film shows the longitudinal rugae of the œsophageal mucosa give way to the irregular mucosal folds of the fundus.

Screening must always be employed in searching the œsophagus for ulcer, as it is important to watch the passage of the barium in various

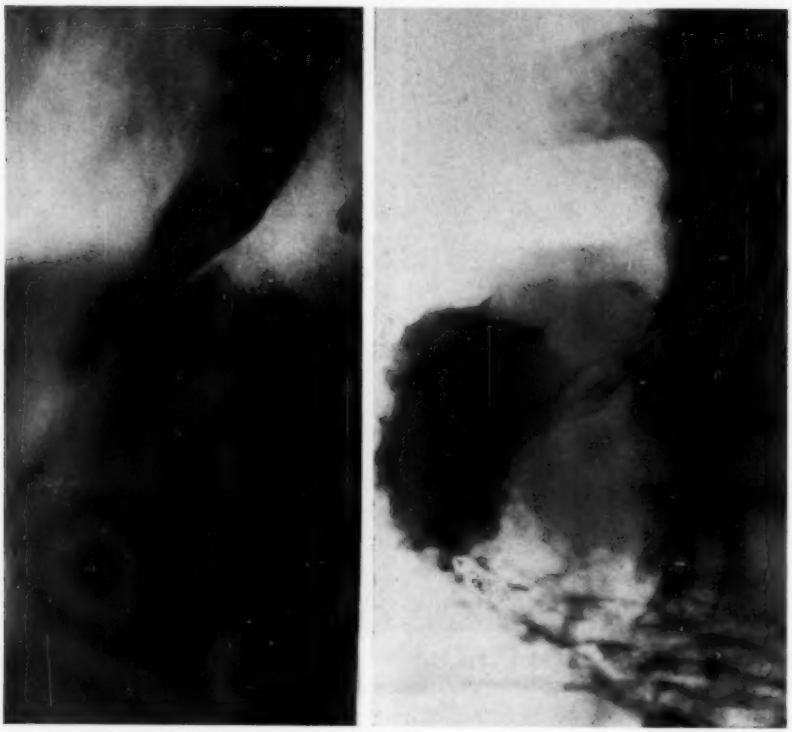

Fig. VII a. VII b.

projections. In addition, the patient should always be examined in the erect as well as the horizontal position. In order to demonstrate a short œsophagus one must place the patient on his right side in the Trendelenburg position. In this position the barium will pass into the supradiaphragmatic end of the stomach, whereas in the erect posture it will weigh the stomach down and exert traction on the hernia which then becomes quite narrow and can easily be overlooked. Repeated examinations are often required before the correct diagnosis is made.

At times it may be extremely difficult to differentiate between an ulcer and a tumour, particularly as the patients are often of the cancer age. In 2 cases our diagnosis proved wrong. The first patient was a female, aged 38, with a history of difficulty in swallowing, pressure behind the sternum, fatigue, and weight loss of one year's standing. Besides, she had regurgitations and melæna. Roentgen examination (Fig.

VI a) showed marked dilatation of the œsophagus which, opposite to the 9th thoracic vertebra, tapered into a narrow canal, about 5 cm in length, which opened into a normal stomach. At the beginning of the stricture there was a slight prominence of the barium which was interpreted as a niche. Œsophagoscopy showed an irregular, readily bleeding tumour at the lower end of the œsophagus, but the biopsy specimen showed inflammatory changes. As the difficulty in swallowing increased, laparotomy was done at the University Hospital, Surgical Department D. It showed a cardiac tumour. On revision of the films (Fig. VI b), it was noted that the outlines of the œsophagus at the site of the stricture were concave in some of the views, a sign of tumour. The other patient was a male of 67 with a brief history of increasing difficulty in swallowing, retrosternal pain, and weight loss. Roentgen examination (Fig. VII a) showed slight dilatation of the oesophagus which narrowed above the diaphragm and opened into the stomach through a quite short canal. A niche, as large as a nut, was seen on the stricture, on the side of the lesser curvature. It was considered to be an ulcer, possibly a tumour. Repeated examination a few days later (Fig. VII b) showed filling defects where the œsophagus opened into the stomach, so it was evidently a case of a tumour. The diagnosis was later confirmed by œsophagoscopy and operation. Reversely, an ulcer may also be misinterpreted as a tumour, as will be seen from case history IV. NØRGAARD published a similar case in 1940.

The roentgen diagnosis can be verified by œsophagoscopy which was performed in 16 of our patients, with a positive result in 11. This accords well with DICK & HURST's statement to the effect that œsophagoscopy may prove a failure, when the œsophagoscope cannot pass the constricted area.

In the course of time various theories have been advanced as to the ætiology of peptic ulcer of the œsophagus. In TILESTON's opinion excessive use of alcohol was of a certain importance. CHEVALIER JACKSON emphasized the significance of focal infection. He found evidence of infection in the teeth, tonsils, or nasal accessory sinuses in 90 per cent of his patients.

Recently DICK & HURST as well as ALLISON have demonstrated the decisive significance of the action of acids on the sensitive œsophageal mucosa. According to ALLISON it is a process of four stages: Œsophagitis, œsophagitis with ulceration, œsophagitis with a chronic ulcer, and finally a healed fibrous stenosis. Acid contact may take place in several ways, for instance by regurgitation of gastric contents. Normally the closing mechanism of the cardia is sufficient and consists, according to DICK & HURST of 3 components: I. Ring-like muscles at the lower end of the œsophagus, acting as a sphincter. II. The oblique opening of the œsophagus into the stomach which forms a sort of valve, further

strengthened by n-shaped muscles in the angle between the œsophagus and the stomach. When the fundus is filled, this valve is pressed toward the œsophageal opening. III. The œsophagus passes through the diaphragm surrounded by strong muscles. During inspiration the negative pressure in the chest and the positive pressure in the abdomen are increased, pressing the cardia and fundus into the thorax, but the strong muscles around the hiatus contract at the same time, thus preventing the appearance of herniation (ALLISON). In cases of a short œsophagus, the interplay between these three factors has been interrupted. In the horizontal position the gastric contents pass into the hernia and further into the œsophagus, as the cardiac sphincter can offer but slight resistance. This regurgitation is easily demonstrated by fluoroscopy. This is, furthermore, the explanation why the symptoms of short œsophagus are intensified in the horizontal position.

In this connection the question as to the ætiology of short œsophagus has been the subject of renewed discussion. Formerly it was thought to be due to deficient development of the œsophagus during fœtal life and hiatal hernia was considered to be a secondary phenomenon, due to the traction exerted by the œsophagus on the stomach. This explanation cannot, however, hold in all cases, as a short œsophagus may frequently be encountered in elderly patients in whom the symptoms have set in at an advanced age. As already mentioned, ÅKERLUND's classification of hiatal hernias comprised a group in which the herniated contents were the cardia and fundus and in which the œsophagus was of normal length. This category, also called sliding hernia, ÅKERLUND found especially in elderly subjects. The cause is a weakening of the muscles around the hiatus œsophageus. As a rule the hernia is visualized only in the horizontal position, as there is apparent reversion to normal in the erect position. In the horizontal position the gastric contents can pass into the hernia and thence into the œsophagus, and if the acid secretion is preserved, there is a possibility that a peptic ulcer be formed in the œsophagus. If such peptic ulcer has persisted for some length of time, it may lead to fibrous changes in the œsophageal wall, causing longitudinal shrinkage which shortens the œsophagus (ALLISON). In ALLISON's opinion the same explanation applies to children, the hiatal hernia being congenital and the short œsophagus a secondary phenomenon.

It is not, however, every case of œsophageal ulcer that is attended with a short œsophagus. Nine of our patients, all older than 15, did not exhibit this combination. Four of these nine patients showed gastric ulcerations localized in the pylorus or duodenum, ulcerations which had given rise to symptoms long before the appearance of the œsophageal lesion. In these cases the gastric lesions were especially characterized by periodical vomiting of acid gastric contents. In that way the acid had

acted on the œsophageal mucosa for a long time, affording an opportunity for the production of œsophageal ulcer.

As already mentioned, one of the remaining 5 patients had 15 years previously suffered from cardiospasm treated with dilatation by the method of PLUMMER. This has presumably damaged the closing mechanism of the cardia which has become insufficient and allowed regurgitation of gastric contents.

Now remain 4 patients with peptic ulcer of the œsophagus who failed to exhibit any œsophageal or gastric changes which might cause regurgitation of gastric contents. The action of acid upon the œsophageal mucosa must therefore have taken place in some other way. Studying biopsy specimens from 7 of the patients with active ulcerations in the œsophagus CHEVALIER JACKSON found ectopic, acid-producing gastric mucosa around the ulcerations. The same observation has been reported by other workers, *inter alia* STEWART & HURST. Although most of the acid is neutralized by saliva, enough appears to remain to produce autodigestion of the œsophageal mucosa and consequently an ulcer (DICK & HURST). It is impossible to state whether this explanation applies to our 4 cases, as no biopsies were obtained.

According to what has been stated above, the only rational way to treat peptic ulcer of the œsophagus is to eliminate the factor which is responsible for the presence of acid in the œsophagus. The treatment in cases of short œsophagus and œsophageal ulcer must therefore be repair of the hiatal hernia. This is not always possible, however, as the changes in the œsophagus may have led to shrinkage of the latter. Operation was performed in 6 of our cases within this group, 4 adults and 2 children. In only 2, one adult and one child, was it possible to reduce the hiatal hernia. As to the remaining 4 operated patients resection of the ulceration was done in 1 and in 3 adhesions were removed. The 12 patients with œsophageal ulcer and short œsophagus who did not undergo operation were treated with dietetic management, dilatation of the œsophageal stricture, or with a permanent duodenal tube. This resulted in most cases in only transitory improvement, and particularly the children have been hospitalized repeatedly. Two patients died. One was a boy, aged 6, in whom the ulceration had led to œsophageal stenosis. As already mentioned, he died after jejunostomy had been established. The other patient was a male, aged 54. He was treated with bougie which, however, brought on abdominal pain, and death was due to peritonitis. Autopsy revealed an ulcer in the lower end of the œsophagus, but no perforation was demonstrable.

In patients who suffer from œsophageal as well as gastric ulcer, removal of the gastric lesion will probably have a curative effect on the œsophageal changes as well. One of the 4 patients in this group was

treated with diet and local applications of silver nitrate with satisfactory effect, and 1 was treated with diet and dilatation with bougie, also with a good effect. In the last 2 cases the changes led to œsophageal stenosis necessitating resection of the strictures, combined with gastric resection in one (Case IV).

If the cause of the œsophageal complaint is neither a short œsophagus nor a gastric lesion, but a possible acid production from ectopic gastric mucosa, the treatment must be diet and perhaps dilatation of the constricted segment of the œsophagus. This was done in our cases within this group, with excellent results in all.

SUMMARY

Twenty-seven cases of peptic ulcer of the œsophagus are reported. The disease was found to be most common among children below 10 years of age and among adults older than 30. In 18 patients the lesion co-existed with a short œsophagus and in 4 with gastric or duodenal ulcerations. The symptoms were vomiting, hæmatemesis, pain and difficulty in swallowing. Characteristic ulcer craters were demonstrated radiologically in 21 patients, all of whom showed a constriction of the œsophagus around the ulceration, in acute cases caused by oedema and inflammatory changes and in chronic cases by fibrous changes. Finally, the author discusses the ætiology, stressing the rôle played by short œsophagus in the production of œsophageal ulcer.

ZUSAMMENFASSUNG

Es wird über 27 Fällen von Ulcus pepticum der Speiseröhre berichtet. Es stellte sich heraus, dass die Krankheit bei Kindern von unter 10 Jahren und bei Erwachsenen von über 30 Jahren am häufigsten vorkam. Bei 18 Patienten war die Krankheit mit kurzer Speiseröhre kombiniert und bei 4 mit Geschwüren des Magens oder Duodenum. Die Symptome waren Erbrechen, Hämatemese, Schmerzen und Schluckschwierigkeiten. Charakteristischer Geschwürskrater wurde bei 21 Kranken röntgenologisch nachgewiesen, und zwar zeigten sämtliche eine Verengerung der Speiseröhre in der Umgebung des Geschwürs, in akuten Fällen durch Ödem und Entzündungsvorgänge und in den chronischen durch fibröse Veränderungen verursacht. Schliesslich bespricht Verf. die Ätiologie und betont die Rolle, die eine kurze Speiseröhre für die Entstehung des Speiseröhrengeschwürs spielt.

RÉSUMÉ

Relation de 27 cas d'ulcère peptique de l'œsophage. On a constaté que l'affection était plus courante chez les enfants de moins de 10 ans et les adultes de plus de 30. Chez 18 malades la lésion coexistait avec un œsophage court, et chez 4 avec des ulcérations gastriques ou duodénales. Les symptômes consistaient en vomissements, hématémèses, douleur et difficulté à la déglutition. On a mis en évidence, radiologiquement, des cratères ulcéreux caractéristiques chez 21 malades, qui tous montraient une sténose de l'œsophage autour de l'ulcération, sténose causée dans les cas aigus par de l'œdème et des altérations inflammatoires, et dans les cas chroniques, par des altérations fibreuses. En terminant, l'auteur discute de l'étiologie, soulignant le rôle joué par la brièveté de l'œsophage dans l'apparition des ulcères à son niveau.

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FROM THE ROENTGEN DEPARTMENT OF THE UNIVERSITY HOSPITAL, OSLO, NORWAY
(CHIEF: PROFESSOR TORLEIF DALE, M. D.)

ON ROENTGEN TREATMENT OF INTRACRANIAL GLIOMAS[1]

by

Arne Engeset, M. D.

The most important group of intracranial tumours is the glioma group. In most clinics they amount to about 50 per cent or more, of the tumour material. The roentgen treatment of intracranial tumours has been studied by various authors in this country: SÆTHRE and JØRGENSEN (63), MONRAD-KROHN and LOSSIUS (43) and REITAN (53). Little attention has been paid to the gliomas by these authors, however.

Early Roentgen Treatment

Following the favourable results reported by NORDENTOFT (44) in 1916 the roentgen treatment of intracranial tumours was advocated as routine method by BÉCLÈRE, as it was considered that this therapy was free from the dangers and encumbrances pertaining to surgical methods. TASSITCH (65), however, in 1925 demonstrated a mortality of 16.9 per cent after roentgen treatment of intracranial tumours.

The following year BÉCLÈRE pointed out that such complications were caused by what he termed »préréaction». Such reaction appeared constantly after adequate roentgen doses, and in some degree was directly proportional to the dosage. The symptoms were due to swelling of the tumour and the surrounding tissues within the unyielding skull caused by the irradiation. This could be verified by measurements of intracranial pressure before and after treatment (23). Others observed increase in volume of existing cerebral prolapses during treatment (55), and others again could report swelling under the bone flap in cases in which decompression had been performed. Experience showed that such reactions were most dangerous in patients with greatly increased intracranial tension.

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Large roentgen doses were the rule in those days. We do not now consider it remarkable if patients died during roentgen irradiation, when it is realized that doses were given of up to 1,360 r, frequently on consecutive days, to patients with high intracranial tension. BÉCLÈRE (6) recommended fractioning of the doses, and held that a reasonable amount of r may be given every day with good result. He proposed that the effect of a *maximum dose* of 227 r every day be tried, which in some cases also may be too high, however.

In recent years great technical and diagnostic advances have been made (8, 12, 27, 32, 51, 52), DANDY's pneumography (15), SCHÜLLER's papers on skull diagnostic (60) and MONIZ's studies on angiography (42). Improved focal diagnosis gave increased technical possibilities for attacking the gliomas. In the past years it has also been possible to secure preoperative type diagnosis of these tumours.

Two main methods of treatment are observed, viz.: BÉCLÈRE (6) was of the opinion that roentgen irradiation should be given on gliomas irrespective of knowledge of localization, size or type of the tumour. Other authors agree with him, especially in cases of cerebellar medulloblastoma. On account of the dangerous complications most authors probably hold the opinion that a decompressive craniotomy should be carried out before radiotherapy to minimize a fatal »prérèaction». After such operative procedure information may be obtained also of the localization, size and type of the tumour.

On Surgical Treatment of Gliomas

In 1928 BAILEY and co-workers (4) drew the conclusion that roentgen therapy of intracranial gliomas should be undertaken only after an attempt has been made to extirpate the tumour when localized or after a decompression has been done in case the tumour cannot be localized. This is according to one school of surgery. In 1940 BAILEY (2) describes a surgeon of another school as one who attempts to estimate the operability of the patient, the size and extension of the tumour, and also its localization. This is of importance when the surgeon has to decide whether to intervene radically, partially, palliatively, or to abstain entirely. If this point of view is followed the number of operations will be less, the operative mortality will be a great deal lower, and the defects provoked by operations fewer.

HORRAX (discussion 30) have seen the best results after radical surgery with extirpation of frontal, temporal or occipital lobes, but he did not perform hemispherectomies, which also have been done by DANDY. He has a mortality of between 26 and 36 per cent.

The gliomas do not metastasize to other organs, but may spread

within the intracranial and intraspinal fluid pathways. The metastases often gather caudally in the spinal canal, and are called, therefore, gravitation metastases. Such spread of the gliomas is often seen in cases with medulloblastomas (4), but may be seen also in other cases of gliomas (9, 17, 59).

The number of metastases seems to increase after operative intervention, and some surgeons therefore abstain from surgery in cases of medulloblastoma. ELSBERG and GOTTEN (19) in 1933 reported a mortality of 36.6 per cent after radical surgery upon cerebellar medulloblastomas. After decompression combined with biopsy, however, the mortality decreased to 13 per cent. TEMPLE FAY (discussion 14) and SACHS (57) dissuade from biopsy also, as they are of the opinion that opening of the subarachnoid space favours the spread of metastases.

After the diagnosis of *glioblastoma multiforme* could be established preoperatively by many authors (20, 26, 33, 54, 68) several surgeons have abstained from surgery in these cases. The operative mortality is high, and the postoperative results, more often than not, poor.

To some degree we may also diagnose the astrocytomas and the oligodendrogliomas preoperatively. The results of roentgen treatment of these tumours may prove to be poor or dubious, and it is relatively fortunate, therefore, that these tumours are better adapted to surgical treatment than the glioblastomas.

Type diagnosis of other gliomas is of no general importance. Some of them may be diagnosed or perhaps suspected to be of a particular type, and the clinical evidence may be of importance (cerebellar medulloblastomas).

The postoperative survival dates reported in 1926 by CUSHING-BAILEY (3) combined with a statistic from TORKILDSEN (67) of the relative incidence of gliomas, may be of interest for comparison with more recent results, and are compiled in the following table:

	Average postoperative survival according to CUSHING-BAILEY	Relative incidence of gliomas in the operative material of TORKILDSEN
	Months	Per cent
Glioblastoma multiforme	12	26.7
Medulloblastoma	2	14.7
Ependymoma	25	6.7
Astroblastoma	28 +	5.7
Oligodendroglioma	66 +	3.8
Astrocytoma	88	33.0

JENKINSON and OLDBERG (30) strongly stress the fact that patients with glioma cannot be cured. They advocate, therefore, conservative

surgical methods, often palliative surgery combined with roentgen irradiation. They believe that with such therapy they usually *increase the patients' subsequent comfort and usefulness*. They state, however, that the majority of their patients die within a period of two years.

Main Features of Roentgen Treatment of Gliomas

In 1928 BAILEY, SOSMAN and VAN DESSEL (4) published the first paper on a large material of *gliomas*, in which all had received adequate irradiation, evaluated according to the new histogenetical classification of BAILEY-CUSHING. They found the following:

Medulloblastoma:	Increased survival from 12 to about 34 months.
Glioblastoma multiforme:	Slight, though favourable effect.
Astrocytoma protoplasmaticum:	Slight, though favourable effect.
Astrocytoma fibrillare:	No favourable effect.
Astroblastoma:	No distinct effect, but should be treated on account of numerous mitoses and recurrences.
Ependymoma:	No effect.

Different degrees of radiosensitivity had been demonstrated for the first time. The variable effect frequently seen of roentgen treatment of tumours with identical histological structure is not difficult to explain. Tumours may block the cerebrospinal pathways, they may show cystic degeneration or there may be hemorrhage. Such complications could certainly cause the symptoms.

To estimate the value of the roentgen treatment various methods were tried. *Clinically* neurological symptoms may be seen to disappear, and potential recurrences may also be seen to react favourably (68). *Pneumographically* it was demonstrable that the dislocation and contortions of the ventricular system disappeared at the same time as the neurological symptoms faded away (56). *Histological* examination before and after the roentgen irradiation showed destructive changes in the tumour area. No investigator found total destruction of a glioma, however. On the contrary, most investigators were able to demonstrate the presence of ample living tumour cells scattered in such areas of distinct destruction. The most sensitive of all gliomas was reported to be the medulloblastoma (1, 13, 64).

Consequently the majority of investigators recommended increasing the roentgen depth dose, and some investigators even tried roentgen treatment of brain tumours in the operating room through the open wound, but not with good results (11, 18).

DYKE and DAVIDOFF (17) in 1942 give 1,000 to 1,400 r through three or more portals, 200 r to each portal daily. As a rule they give three series. The interval between the series is usually about two months. On different tumours they may give 4 or 5 series, and they may reach a total roentgen dose of 25,000 r measured in air in one patient. Still higher doses are given by FRIED (22). He states that hair will reappear after doses of 25,000 r. A woman, 23 years of age, was treated for an inoperable glioma in the precentral region. She got a total roentgen dose of 32,649 r through 5 portals against the tumour. She survives about three years after the treatment. She bicycles, swims and works as a shorthand typist.

The highest roentgen dose reported is that used by KAPLAN (31). In the course of 22 months he treated a man with 42,000 r given through 6 portals against an inoperable glioma. The dose was measured in air. KAPLAN is of the opinion that the growth of the tumour was arrested, and he also observed a favourable influence on the epileptic seizures of the patient.

Some investigators (17, 47, 45) have tried to find an *optimum* roentgen dose. Some suggest doses between 5,000 and 10,000 r against gliomas (17). Others suggest doses of 6,000 r for astrocytomas, but prefer 7,500 r in cases of glioblastoma multiforme (47). The statistics of PEIRCE and his colleagues seem to verify that such dosage may increase the postoperative survival period.

About Irradiation Injuries

During recent years reports of probable roentgen injuries of the brain have been accumulating. O'CONNEL and BRUNSCHWIG (45) have four cases, WACHOWSKY and CHENAULT (69) six cases, among others. After a total roentgen dose in tumour of 6,100 r initial good effect could be seen, as long as for 8 years. In some cases, however, the favourable effect lasted only so many months. But the important point was that the signs of roentgen degeneration of the brain could be postponed as long as 8 years before they became manifest.

In some cases the symptoms of roentgen degeneration may be restricted to slight visual abnormalities and cramps. In other cases great cerebral lesions could be seen, and the patients died. Some of the patients developed into a »vegetative status». In such patients the decompression area may be seen to be sunken, contrary to the bulging which is usual when tumours are recurring.

One patient, a woman, received a *tumour dose* of 4,403 r (69) and returned to her normal level of mentality. After about 7—8 years she developed convulsions and was rapidly in a vegetative status.

In the literature one may find many cases of probable radiation injuries (35, 38, 50, 58) and also injuries of the medulla spinalis (50). Osteonecrosis of the cranial bone after roentgen irradiation of a brain tumour may also be seen (10), but we have not yet seen any report of combined cerebral injury in such cases. They constitute no contraindication, therefore, against roentgen irradiation of intracranial tumours.

Roentgen Therapy Alone

On account of the high mortality and the risk of metastasizing following intracranial surgery of gliomas SOSMAN, CUTLER and VAUGHAN (14) recommended treating cerebellar medulloblastoma with roentgen rays only. Any mortality following roentgen treatment should be very low, and the results of roentgen treatment was expected to be better than surgery alone, and as good as surgery and roentgen rays combined.

SOSMAN holds the opinion that the clinical diagnosis of cerebellar medulloblastoma, especially in children, is characteristic. Roentgen treatment may be given to a selected group of patients, and an almost miraculous improvement ten days after such treatment should give confirmation of the diagnosis, almost as certain as a biopsy.

The roentgen treatment should be correctly given to obtain the best possible results. First treatment of the tumour area, subsequently of the basal parts of the cerebrum and the medulla spinalis, the latter regions in order to destroy early development of metastases.

One of his cases, treated with roentgen rays alone on a cerebellar medulloblastoma, survives after nine years. She is working as a nurse.

One case of ependymoma has been reported, however, which has shown »miraculous» improvement after being treated by the method of SOSMAN, with a survival of four years (50). This is contrary to the conclusion of BAILEY and collaborators, that *ependymomas* are resistant to roentgen rays.

Roentgen Treatment of Animals

LYMAN, KUPALOV and SCHOLTZ (35), DYKE and DAVIDOFF (17) have discussed previous literature. The results of earlier studies of roentgen treatment of animals may be summarized as follows:

Roentgen treatment of various animals may produce degenerative alterations in the nervous system if sufficiently high dosage is applied. The »hemato-encephalic barrier» is influenced more by fractional roentgen treatment than after large single doses (40, 41). Children are more sensitive and more exposed, therefore, to roentgen injuries than adults (24). Such injuries may develop during long periods, months and even years, before being manifest.

DAVIDOFF, DYKE, ELSBERG and TARLOV (16) treated the brain of the *Macacus rhesus* directly through the open wound, in the operating room, and found the following:

After a dose of 1,000 r the clinical and physiological effect was negligible. The animals receiving 2,000 to 3,000 r on the motor area of the brain, developed a hemiparesis after several months, while those receiving a dosage of 4,000 r or more on a cerebral hemisphere were stricken with a contralateral paralysis within the first twenty-four hours. None of the animals in which the cerebellum was irradiated, developed any immediate symptoms, but in two of them (dosage 4,000 to 5,000 r) cerebellar disturbances appeared after from three to five months.

In all the animals which died, there were well-marked changes in the central nervous system.

The two factors which seemed to play a part in governing the intensity of the histological changes, were the dosage of roentgen rays and — to a less extent — the time interval between irradiation and autopsy. It seemed, both on clinical and histological grounds, that the destructive changes were to some extent progressive, although the period of time during which such progressive changes may occur has not been determined.

Considering the earlier reports of degenerative changes in human patients after eight years, I have the impression that the investigations of animals after irradiation has been insufficient. Most of such investigations have been ended after a few months, and the effect of fractional irradiation has not been studied much as far as I know.

Some investigators have studied the effect of irradiation on the production of cerebro-spinal fluid (25, 28, 37, 61). SKEFER (61) holds the opinion that small irradiation doses have a restraining effect. Large doses may first have a stimulating effect, but later the restriction of the production of cerebro-spinal fluid may be still greater. This may prove to be of practical importance during treatment of patients with increased intracranial tension.

Own Material

The following material has been collected among cases of glioma in the period 1932 to 1946. All patients have been treated with roentgen rays in the Department of Roentgenology of the University Hospital of Oslo. Most of them have been operated upon in the Department of Neurology by TORKILDSEN. Some of the patients have been operated on in the Surgical Department B by Professor R. INGEBRIGTSEN. A few patients have received roentgen treatment only.

In most patients the tumour has been removed in part, in some

ases a biopsy only has been taken. In other cases a palliative operation as been performed. Cases subjected to insufficient follow-up examination only have been excluded from the material. All histological diagnoses n the first group of patients, 39 cases of glioma, have been controlled by J. CAMMERMEYER.

No. of Cases	Type Diagnosis	Sex		Age	Average
		M	F	Years	Age
18	Glioblastoma multiforme	9	9	19—56	43.4
12	Astrocytoma	6	6	13—48	38.3
4	Medulloblastoma	1	3	6—8—16—19	
2	Oligodendroglioma	2	0	35—39	
2	Astroblastoma	1	1	6—30	
1	Ependymoma		1	22	

A second group consists of 7 patients with tumours in the third ventricle and the pineal region. They are diagnosed pneumographically, and treated palliatively with ventriculocisternostomy by the method of TORKILDSEN.

As a third group we have some cases of cerebellar medulloblastoma. They are diagnosed clinically, and treated with roentgen therapy only, by the method of SOSMAN.

Glioblastoma Multiforme

All these patients are dead. Average survival time was 8.9 months, which is a little lower than in other statistics. The difference, however, is not great. Some of the patients showed a slightly favourable course after the roentgen irradiation, but none of these patients were able to work. For a short while some of them were able to dress and eat without assistance, but most of them got worse with cramps, hemiparesis, and so forth.

The total roentgen dose in air given to these patients varied between 600 r and 10,200 r.

Astrocytoma

8 of 12 patients survive after 26, 34, 40, 54, 84, 84, 100 and 174 months respectively. All of them feel better after the operation and the roentgen treatment. Three patients were fully fit for work. Five patients were able to work now and then, and three others were able to dress, wash and eat without assistance.

All patients had some sort of sequels. Some of them had slight epileptic fits only; most of them, however, had various other lesions such

as aphasia, cramps and dementia. Visual disturbance was not unusual. One patient, for instance, living 84 months after treatment, was blind and had epileptic fits. He could not help himself, and had to be nursed by his mother. Another patient, living as long as 174 months, was not able to walk outside his flat, but could wash himself, but was not able to do his hair.

Total doses in air given to these patients varied between 1,360 r and 16,150 r, the latter, largest, dose given to a patient with recurrence.

In agreement with earlier statistics, patients with astrocytoma have a much longer survival time than patients of the former group of glioblastomas. The tumours are of a more benign nature. The subjective and objective recovery after treatment is indubitable, and perhaps surgery is most effective in this respect. In spite of the fact that these patients have a long survival time without any sort of treatment, we have the impression that favourable effect may be obtained by combined surgical and roentgenological treatment.

Astroblastoma

A boy of 6 years, is living 70 months after operation and roentgen treatment. He is attending school, and his general condition is excellent (April 1948). Total roentgen dose in air 9,900 r.

Another patient, a 30-year-old female, died 36 months after operation and roentgen treatment. She was unable to work fully, but improved during 12 months, and could then dress, eat and do her hair without help. Postoperatively she had cramps and hemiparesis, however. Total roentgen dose in air was 2,460 r. It is our impression that the first patient, the boy, has had a very comfortable life after the treatment, and this is also the opinion of his father, a parson.

Oligodendroglioma

One patient, a female 35 years old, died 48 months after operation and roentgen treatment. She was working the first 6 months, but later she declined slowly. Total dose of roentgen in air 10,200 r.

The second patient, a 39-year-old female, was admitted into the hospital with major neurological lesions (Fig. 1 & 2). Pneumographically was found a great expanding lesion in the left hemisphere. Her condition was poor, and as the tumour was suspected to infiltrate the central parts of the brain operative intervention was not thought feasible. After roentgen treatment the neurological symptoms disappeared, and pneumographic control 6 months later showed that the displaced ventricular system had regained its normal position. She was almost symptom-free

Fig. 1. Female, 39 years of age. Ventriculography 26th June 1943. Expanding lesion in the left hemisphere, probably with central infiltration.

Fig. 2. Same case: Ventriculography 10th November 1943. The expanding lesion has disappeared after roentgen treatment.

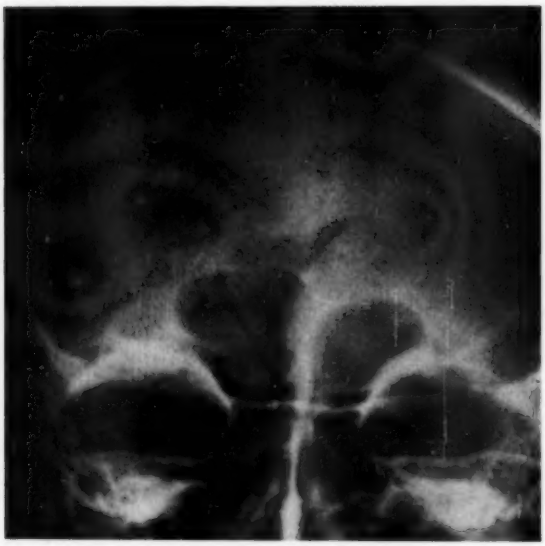

Fig. 3. Ventriculography 6th November 1945. After two years improvement, recurrence, larger than before, but in the same localization. Autopsy: Oligodendroglioma.

and in working condition for the two following years, before a recurrence took place. Fresh pneumographic control showed an expanding lesion, again with the same localization (Fig. 3). Surgery did not help her, and she died. Histological investigation showed that the tumour was an oligodendroglioma. It is evident that some cases of oligodendroglioma may be treated by roentgen irradiation with some degree of success. Roentgen treatment of the recurring tumour was not tried in this case.

Cerebellar Medulloblastoma

Two children survived for 17 and 24 months respectively. A 16-year-old girl had a survival time of 30 months, and a woman, 19 years old, is still living 137 months after operation and roentgen treatment. She is doing typewriting, knitting and weaving, but is almost blind, as she was also before the operation and roentgen treatment. On October 17th 1936 TORKILDSEN removed partially a tumour in the fourth ventricle and the left cerebellar hemisphere. Postoperatively she got a total roentgen dose in air of 13,995 r directed through 5 portals, one over the cerebellum 5,115 r, one on each side of the cerebrum 1,800 r, and finally through 2 portals into the spinal medulla 2,250 r.

Favourable effect of roentgen treatment of cerebellar medulloblastoma has been obtained as far back as the year 1926 (46).

The medulloblastoma has been among the most malignant of the gliomas, but in recent years reports have been accumulating which seem to indicate that medulloblastomas in adults have a better prognosis than in children, and some authors are of the opinion that they are more common in adults than we have formerly realized (62). Lately have been reported survival after roentgen treatment of 17 and 19 years respectively (29, 49). While the cerebellar medulloblastomas in children are characteristically located in vermis cerebelli, in adults they are frequently located in the cerebellar hemispheres. Our patient has not received such high roentgen doses as some authors advocate, but the result, a survival of more than 12 years, is very satisfactory.

Another patient, a boy six years old, with cerebellar medulloblastoma was operated upon. The first time only an exploratory craniotomy was performed. During the second operation two months later, the surgeon could ascertain metastatic spread of tumour tissue in the scars after the first operation, also outside the cranium. This fact shows that evidently operative intervention may cause spread of a tumour, which normally almost never is observed outside the central nervous system. Also supratentorially many metastases were found.

In recent years we have treated many such patients by the method of SOSMAN, with roentgen rays only. The results have been encouraging. A girl, 3 years old, had declined during 5 months. She was pale and tired, and developed ataxia. She was admitted to the Neurological Department in November 1946, with frequent periods of vomiting, unsteady gait, and papilloedema of 2 diopters. The neurosurgeon in charge, G. RØVIG, made the clinical diagnosis of cerebellar medulloblastoma. As the patient also suffered from pertussis and was in poor general condition, operative intervention was not considered advisable. It was decided to try roentgen treatment.

The result was almost »miraculous» after 18 days. All symptoms disappeared in the course of a few weeks, and she is still in excellent condition, more than 29 months after the roentgen irradiation. She got 4,600 r in air through two portals over the cerebellum, 1,600 r through one portal each over the basal cisterns and the cerebrum, and 2,000 r divided between two portals against the spinal medulla. On the whole perhaps not very high doses, but the result could not be better.

Tumours in the Pineal Region and in the Third Ventricle

These tumours have been diagnosed pneumographically and clinically, and they have been operated upon by TORKILDSEN. His operation ven-

triculocisternostomy has been performed. Histological examination is lacking according to circumstances. There are six patients between 1(and 44 years of age, with survival periods varying between 4.5 month: up to more than 100 months. Two patients surviving after 60 and 10(months respectively are fully fit for work. One of them, a boy, 16 year: of age, has been treated by roentgen rays for 21 months, and has reacte more and more favourably after each treatment. We may assume accordingly that the irradiation, especially in this case, has been distinctly successful.

In the monograph of TORKILDSEN (66) is reported also a case which died after the ventriculocisternostomy, and in which post-mortem examination demonstrated a medulloblastoma in the posterior part of the third ventricle. It may be assumed that a series of preoperative roentgen treatment in this case might have been a potential means of recovery. It has been pointed out by SJÖQUIST that credit must also be given to roentgen treatment for the beneficial effect of this operation. It is a fact that most of the patients with the longest periods of survival after this operation have also received roentgen irradiation.

Late Irradiation Injuries

A 21-year-old male for three weeks had shown signs of a cerebellar lesion. Pneumographically an expanding lesion was demonstrated in the left hemisphere, probably also with a central localization. Due to this site the patient was not subjected to operation. In the course of 16 months he received five series of roentgen irradiation. The total dose amounted to 30,800 r in air, the last series 4,500 r supervoltage.

He was tired after the different series of treatment, but recovered fairly well every time. He felt fit for work and had no headache. After 26 months he received an additional supervoltage irradiation of 6,450 r, during which treatment he suddenly one day developed right-sided hemiplegia and dysphasia. He died three weeks later. J. CAMMERMEYER found necrosis corresponding to the part of the brain which had received roentgen treatment, and suggested that the changes may be due to irradiation injury.

In spite of the favourable effect of similar high doses in inoperable cases reported from various clinics, I feel convinced that this patient had received too much irradiation. A total of 37,250 r is probably too much, even though the tumours are inoperable.

»*Préréaction*» (*Béclère*)

To avoid the dangerous »préréaction» one has to start with very small irradiation doses, especially when no decompressive craniotomy has been

performed and the intracranial tension is high. We have treated patients suffering from cerebellar medulloblastoma with roentgen irradiation only, in spite of the fact that they have papilloedema of 6 diopters. In such cases we start with 25 r each day for the first 4 or 5 days, and according to the condition of the patient we increase the roentgen dose to 50 r up to 100 r daily; in the course of two weeks we may reach a daily dose of 200 up to 300 r. Even by slight signs of »prréaction» we postpone the treatment for a day or two and in this way may practically exclude the risk of »prréaction» which, as we know, may prove fatal.

To avoid »prréaction» some clinics do not start roentgen treatment before 6 weeks after the operative intervention. Thus they may avoid *postoperative* complications (48). In spite of this routine they start with small doses of 50 r each day. In other hospitals irradiation is started 3 days after the operation, which we do also. Occasionally we have to try treatment in patients who have no other hope of recovery. Some particularly poor patients we have observed to get worse after irradiation, and we have seen cases in which irradiation may have been one of the provoking factors in fatal cases. BÉCLÈRE's trial dose of 227 r (6), is much too high in such cases, but 25 r every other day must be considered safe. These doses may seem too small to have any beneficial effect, but we have seen favourable effects also after such small doses.

The practice of delaying irradiation until six weeks have elapsed after the operation, is tempting, no doubt, but in our widespread country, where the patients may have their homes in remote parts, even several days' travel from the hospital, and considering the scarcity of hospital beds, this is not practicable. Most patients — if not all — may be treated cautiously with small doses for the first two weeks on proper indications.

Our Technique

Kilovoltage 170. Milliampère 6. Thoræus filter routinely. In case of troublesome children we use 0.5 mm Cu to shorten the time of treatment. Routinely we use 3 or 4 portals to gliomas. We try to obtain a *tumour dose* of 5,000 r or a little less in children. Dose per session from 25 r to 2×150 r daily. I consider that reports from hospitals working with different intensities may show almost the same results as ours. HOLFELDER (27) utilizes a machine and a system which delivers 90 r per minute, while we work with an intensity of 11 r per minute. Small series, repeated frequently, as used by DYKE and DAVIDOFF have been abandoned by PEIRCE, and coworkers. We use almost the same technique as these latter investigators. It is only exceptionally that doses exceeding 12,000 r measured in air, have been used in our material.

Comments

1. For many years *radical treatment* of gliomas by surgical and roentgenological methods, has been tried in order to *destroy all tumour tissue and cure the patient permanently — but without success.*

Improvement may be obtained, however, of shorter or longer duration in many cases. The object now is to endeavour to achieve optimum results with the aid of optimum irradiation dosage and adequate technique.

2. As it now seems to appear from the literature that degenerative effects in the cerebrum may occur after tumour doses of about 6,000 r, great care must be shown not to apply large doses of irradiation on highly sensitive parts of the brain (the dysphasia region, the visual area, and the motor region) without realizing what to gain and what to lose.

3. As far as the author is aware total destruction of a glioma has been reported only once, in which case all cerebral substance in the region was also destroyed, however (39). The suggestion of BAILEY to produce destruction of the frontal lobes in desperate cases by giving large irradiation doses — as a kind of leucotomy — so far is only a subject for discussion.

4. In our material we have seen an indubitably favourable effect of roentgen treatment of an oligodendroglioma, clinically and pneumographically.

5. One case of cerebellar medulloblastoma, a female, survives 137 months after combined surgical and roentgenological treatment.

6. In several cases of cerebellar medulloblastoma in children we have encouraging results with roentgen treatment only, by the method of SOSMAN. One patient survives after 29 months, symptom-free. During the same period no recurrences were observed in other patients similarly treated.

7. After a total dose of 37,255 r against the left hemisphere in the course of 26 months, we have seen a probable case of injury to the treated area of the brain.

8. When palliative surgical treatment is performed in cases of glioma on the basis of clinical and pneumographical signs, the possibility of preoperative or postoperative roentgen treatment should be discussed.

SUMMARY

The literature on roentgen irradiation of gliomas is discussed on the basis of a material of about 50 cases of glioma at the University Hospital of Oslo, Norway, during the period 1932—1946 inclusive. All these patients have received roentgen treatment, and the majority have been operated upon.

The favourable effect of irradiation on *cerebellar medulloblastoma*, by the method of SOSMAN as well as by combined operative and roentgenological treatment, is emphasized.

One case is recorded with probable irradiation injury of the brain after a total dose of 37,250 r against the left hemisphere.

In order to avoid the dangerous »préréaction» very small initial doses should be given for two weeks. Daily doses as small as 25 r the first days are recommended, especially in cases in which decompressive craniotomy has not been performed.

ZUSAMMENFASSUNG

Das Schrifttum über die Röntgenbestrahlung von Gliomen wird an Hand eines Materials von etwa 50 Gliomfällen aus der Universitätsklinik in Oslo, Norwegen, aus den Jahren 1932—46 besprochen. Alle diese Kranken bekamen Röntgenbehandlung, und die Mehrzahl wurde operiert.

Die günstige Wirkung von Bestrahlung von *Medulloblastomen des Kleinhirns* nach der SOSMAN'schen Methode sowie von kombinierter operativer und röntgenologischer Behandlung wird hervorgehoben.

Es wird über einen Fall berichtet mit wahrscheinlicher Strahlenschädigung des Gehirns nach einer Gesamtdosis von 37,250 r gegen die linke Hemisphäre.

Um die gefährliche »Vorreaktion» zu vermeiden, müssen zwei Wochen lang sehr kleine Anfangsdosen gegeben werden. Es werden in den ersten Tagen tägliche Dosen von nur 25 r empfohlen, besonders in Fällen, wo keine entlastende Kraniotomie vorgenommen worden ist.

RÉSUMÉ

Discussion de la littérature consacrée à la radiothérapie des gliomes, en se basant sur un matériel d'environ 50 cas de gliomes observés à l'Hôpital Universitaire d'Oslo, Norvège, de 1932 à 1946 inclusivement. Tous ces malades ont reçu un traitement aux Rayons X, et la plupart ont été opérés.

L'auteur souligne les effets favorables de l'irradiation sur les *médulloblastomes cérébelleux*, tant par la méthode de SOSMAN que par la combinaison de l'opération avec le traitement radiologique.

Il rapporte un cas ou le cerveau a été probablement lésé par l'irradiation, après administration d'une dose totale de 37,250 r à l'hémisphère gauche.

Afin d'éviter la dangereuse »préréaction» on ne devrait donner que de très petites doses initiales pendant deux semaines. Des doses journalières n'excédant pas 25 r sont à recommander pour les premiers jours, spécialement dans les cas où l'on n'a pas exécuté de trépanation décompressive.

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FROM DET NORSKE RADIUMHOSPITAL, OSLO (HEAD: DR. MED. R. BULL ENGELSTAD)

INTRAORAL MUCOUS- AND SALIVARY GLAND MIXED TUMORS[1]

by

Andreas Hobæk

Although mixed tumors of the large salivary glands are well known both in the clinic and in pathological anatomy, they can hardly be said to be really frequent tumors. The intraoral mucous- and salivary gland tumors, on the other hand, however, are decidedly less known, but have, owing to their characteristic clinical picture, greater claims on our interest than has hitherto been the case. Yet these tumors are so rare, that outside of special tumor clinics there is no opportunity of collecting any great material. Hitherto only 4 to 5 collections of such tumours have been published. In the present work 33 cases in all of intraoral mucous- and salivary gland tumors treated at Det Norske Radiumhospital (D. N. R.) between 1932 and 1945, will be reported. During the same period 246 tumors in the large salivary glands have been treated at the hospital. Thus in this material the extraoral localization of mucous- and salivary gland tumors are about 8 times as frequent as the intraoral one.

It is now generally accepted that mucous- and salivary gland tumors are of an epithelial nature, but the question as to the genesis of these tumors is still pending. From different quarters it is still maintained that they develop from embryonal branchial anlage in the same way as branchiogenic tumors. It is assumed that the cell colonies are isolated already in the first few fetal weeks, when the cells still possess the power of segregating cell structures belonging to all three primary germ layers. Recently HELLWIG (1) has maintained, on the basis of embryological studies, that these tumors develop from »misplaced elements of the notochord» (chorda dorsalis).

In connection with the assumption that mucous- and salivary gland tumors are of a purely epithelial nature, a number of authors maintain that the development of tumors takes place from segregated embryonal glandular epithelium, which is assumed to have been isolated so early,

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that it controls the possibilities of developing into odontogenous, glandular or squamous epithelium. This is thought to explain that in the mandible where the tendency of differentiation of the epithelium has a decidedly odontogenous direction, mainly tumours of the type of adamantoblastomas are found, while in the palate, where the differentiation of glandular tissue is the rule, mostly tumors of a glandular structure are found.

The theory of the genesis of the tumors of the mucous- and salivary glands that seems to be most widely spread, explains the development of the tumors, not from any particular embryonal body of cells, but from the fully developed glandular epithelium or the epithelium in the outlets of the glandular ducts. It is assumed that the epithelium grows into the surrounding connective tissue, and through secretion of mucous material causes the connective tissue to change into myxomatous tissue, which, through organization, forms the so-called »chondroid» tissue. NORRENBROCK (2) has tried to apply SPEMANN's theory of organization to the epithelium in the mucous- and glandular tumors, and explains the occurrence of the peculiar mixture of tissue structures seen in these tumors, as either a transformation of the connective tissue through the accumulation of epithelial secretory products, or a direct changing of the mesenchyme into hyaline, myxomatous and »chondroid» tissue.

The term »mixed tumors» introduced by MINNSEN (3) has now been generally adopted not only in clinical but also in pathological terminology. As only few tumors included in the group of mixed tumors of the mucous- and salivary gland type, do not show more or less distinct signs of a mixed character, it seems necessary to adhere to this term, although it can hardly be said to simplify the nomenclature. As this has been built on purely morphological data, new aspects are constantly cropping up, and, particularly where this group of tumors is concerned, the terminology is, at the present time, so confusingly multifarious and complex, that a direct comparison between materials that are published, can only be made with difficulty. Thus two subgroups of mucous- and salivary gland tumors have recently been added to the group, namely the papillary cystadenoma lymphomatosum (Warthin's tumor) in the gl. parotis, reported by MARTIN & EHRLICH (4), and the mucoepidermoid tumor described by FOOTE & BECKER (5), which is assumed to originate from the epithelium of the glandular ducts, and histologically is built up of epidermoid cells and mucin-producing tumor-cells arranged in alveolus-like fashion.

Several attempts have been made to establish a more uniform and applicable nomenclature for the purpose of collecting all tumors originating in the large and small salivary glands (mucous glands in the mucous membrane of the superior respiratory and digestive tracts) into one large and comparatively well defined group. In 1935 AHLBOM (6) in collaboration with REUTERWALL (7) drew up the following system of classification

(given here in a somewhat simplified form), on the basis of MASSON's (8) and KROMPECHER's (9) works and after careful histological, clinical and therapeutic studies of the extensive material of the Radiumhemmet of mucous- and salivary gland tumors:

I. So-called Mixed Tumors { fibroepithelial, fibromyxoepithelial, fibrochondromyxoepithelial } Benign, semimalignant or malignant.

II. Adenoma . . . Benign, semimalignant or malignant (predominantly adenocarcinoma).

III. Papillary cystic adenoma . . (Benign), semimalignant or malignant.

IV. Basalioma { 1. predominantly cylindromatous. 2. — » — solid. } (Benign), semimalignant or malignant.

V. Predominantly epidermoid cancer.

VI. Slightly differentiated or undifferentiated epithelial tumor.

VII. Fibromyxo-sarcomatous tumor (without definite epithelial structures).

According to AHLBOM »the group is made up partly of tumors which have been called 'tumors of the large salivary glands of the mouth' or 'salivary gland tumors', and partly of similar tumors which occur particularly within or in the neighbourhood of mucous membranes provided with serous, sero-mucous and mucous glands».

The classification into a benign, semimalignant and a malignant tumor group has been made on the basis of clinical and histological data. The appositeness of keeping up a semimalignant undergroup of these tumors may be discussed. Thus MARTIN (10) maintains: »The designation of a semimalignant group is obviously either a frank or unwitting admission of the gradual transmission or intermediate stage, in which the diagnosis is uncertain.» Although it is a fact that semimalignant mucous- and salivary gland tumors in most cases in the course of time become manifestly malignant both cellular-morphologically and clinically, we have found it to be of advantage at the D. N. R., where Ahlbom-Reuterwall's principle of classification has been applied since 1935, to keep up the semimalignant group for the sake of collaboration between the clinical and the pathological departments, as a considerable number of mucous- and salivary gland tumors belong to this category. MARTIN points out that mucous- and salivary gland tumors show a gradual transition from decidedly benign tumors via the semimalignant stage to the decidedly malignant tumors. AHLBOM, however, has strongly emphasized that at the Radiumhemmet they have never been able to demonstrate that a histologically truly benign tumor of this type has later changed character,

Table No. 1

Sex	Age	Site	Histology	Surgery	Radio-therapy	Recurrences	Metastases	Results
♀	68	Palatum durum	Basalioma, cylindr. semimalignant.	0	Roentgen, intraoral tube 4500 r.	0	0	Symptomfree 2 years
♀	34	»	Mixed t. fibromyxoepithel. Semimal.	0	1) Roentgen, intraoral tube 3600 r. 2) Telerad. 1 portal 4080 r	0	0	Symptomfree 2 years
♀	61	»	Basalioma, solid, semimalignant.	0	Surface radium, 4080 r.	0	0	Symptomfree 11 years
♂	58	Palat. dur. et molle	Basalioma, solid malignant.	Extirp. tum. Recurrences.	1) Telerad. 3 portals 4080×3 r 2) Surface rad. 3360 r.	+	To submax. lymph-node (verified)	No growth of tumor remnants in 2 years of observation.
♂	45	Palat. dur. invading antrum Highm.	Basalioma, cylindr. semimal.-malign.	Resect. maxillae dext.	Cavitary rad. 3630 r. Roentgen 3 portals, 3000 r×3.	0	0	Symptomfree 3 years
♀	60	Palatum durum	Mixed t. fibroepithel. semimalignant.	Extirp. tumoris.	Surface radium, 4300 r.	0	0	Symptomfree 11 years
♀	35	»	Basalioma, solid malignant.	0	1) Roentgen, intraoral tube 3500 r. 2) Telerad. 2 portals, 4080 r×2.	2 years after 1st treatment	0	Symptomfree 2 years after sec. treatment.
♀	66	»	Basalioma, cylindr. semimalignant	0	Roentgen, intraoral tube 3500 r. intratumoral rad. 2160 mg. h.	0	0	Tumor remnants, gradullay disappearing. Symptomfree 3 years.
♂	70	Buccae	Mixed t. fibroepithel. benign.	Extirp. tumoris.	Surface radium 3600 r.	0	0	Symptomfree 5 years
♀	58	Palatum durum	Basalioma, cylindr. semimalignant	»	Roentgen, intraoral tube 3500 r.	0	0	Symptomfree 5 years
♀	35	Labium inf.	Basalioma, cylindr. semimalignant.	»	Surface radium 3250 r.	0	0	Symptomfree 7 years
♀	45	Palatum durum.	Papillary cystic adenoma. Semimalignant.	»	Roentgen, intraoral tube 3500 r.	0	0	Symptomfree 2 years
♀	80	Buccae	Basalioma, cylindr. semimalignant.	»	Teleradium 1 portal 4080 r.	0	0	Symptomfree 2 years
♂	34	Palatum molle	Mixed. t. fibromyxoepithel. Semimalign.	»	Teleradium, 1 portal, 4080 r.	0	0	Symptomfree 3 years.
♀	70	Basis linguae	Mixed t. fibromyxoepithel. semimalign.	0	1) Roentgen, 2 portals 3500 r×2. 2) Telerad. 2 portals, 3080 r×2.	Tumor remnants	0	Tumor remnants unchanged 2 years after sec. treatment.
♀	71	Palatum durum	Basalioma, solid, malignant.	0	1) Intratumoral radium, 3638 mg.h. 2) Teleradium, 2 portals 1900 r×2.	Recurrence 4 years after 1st treatment	?	Died 5 years after last treatment.
♂	72	»	Mixed t. fibroepithel. semimalignant.	Extirp. tumoris	Preoperative telerad. 2 portals, 4360 r×2.	0	0	Symptomfree 7 years
♀	61	Palatum durum	Basalioma, cylindr. semimalignant.	Extirp. tumoris	Surface radium 4100 r.	0	0	Symptomfree 11 years.
♀	60	Palatum	Mixed t. fibroepithel.	Resect. max-	Cavitary radium 3660 r. Roentgen	?	?	Not controlled. Died 18 months

♂	72	»	Mixed t. fibroepithel. semimalignant.	Extirp. tumoris	Preoperative telerad. 2 portals, 4360 r×2.	0	0	Symptomfree 7 years
♀	61	Palatum durum	Basalioma, cylindr. semimalignant.	Extirp. tumoris	Surface radium 4100 r.	0	0	Symptomfree 11 years.
♀	60	Palatum durum invading antrum Highm.	Mixed t. fibroepithel. malignant.	Resect. maxillae dext.	Cavitary radium 3660 r. Roentgen 3 portals, 2100×3 r.	?	?	Not controlled. Died 18 months after treatment.
♀	43	Oropharynx	Basalioma, solid, semimalignant	Extirp. tumoris	Teleradium, 2 portals 4050 r×2.	0	0	Symptomfree 5 years.
♂	72	Buccae	Mixed t. fibromyxoepithel. Benign.	»	Teleradium, 1 portal, 4080 r.	0	0	Symptomfree 10 years.
♂	30	Palatum molle	Mixed t. fibromyxoepithel. Malignant.	0	1) Roentgen, 3 portals, 3250 r×3. 2) Teleradium. 1 portal 4080 r.	Tumor remnants	?	Slight reduction after 1st treatment, none after 2nd treatment. Died 5 months after last treatment.
♀	67	Palatum durum	Mixed t. fibromyxoepithel. Semimalign.	0	1) Roentgen, 2 portals, 3500 r×2. 2) Intratumoral radium, 2400 mg.h.	0	0	Marked reduction, tumor gradually diminishing in the course of 3 years. Symptomfree 6 years.
♂	67	Tonsil	Basalioma, solid, malignant.	Extirp. tum. 20 years before treatment.	1) Teleradium 4200 r. 2) Roentgen, 2 portals, 1400 r×2.	Tumor remnants	To submax. lymphnode (verified).	Slight reduction. Died 2 years after treatment.
♀	80	Palatum molle	Basalioma, cylindr. semimalignant.	Electrocoagulation after irradiation	1) Teleradium, 2 portals, 2230 r×2. 2) Teleradium, 1 portal 4260 r.	Tumor remnants	0	Symptomfree 10 years.
♀	48	Palatum durum	Basalioma, cylindr. semimal.—malign.	Extirp. tumoris	1) Teleradium, 2 portals, 3080 r×2. 2) Teleradium, 2 portals, 2330 r×2.	Recurrences	?	Died 7 years after start of treatment.
♀	54	Basis linguae	Basalioma, cylindr. semimal. malign.	0	1) Roentgen, 2 portals, 4200 r×3. 2) Teleradium 2330 r.	Recurrences after 4 years	To submax. lymphnode	Died 5 years after start of treatment.
♂	73	Regio sublingualis	Mixed t. fibromyxoepithel. Semimal.	0	Teleradium, 2 portals, 4050 r×2.	Tumor remnants	?	Moderate reduction. Died 2 years after start of treatment.
♀	66	Palatum durum invading antrum Highm.	Basalioma, cylindr. malignant.	0	Roentgen, 3 portals, 3500 r×3.	Tumor remnants	?	Marked reduction. Died 5 years after start of treatment.
♂	63	Palatum molle	Slightly differentiated epithelial tumor. Malign.	0	Teleradium, 2 portals, 4260 r×2.	Recurrences	?	Slightly radiosensible. Died 18 months after start of treatment.
♀	61	Tonsil	Basalioma, solid, semimalignant.	Extirp. tumoris	Roentgen, 2 portals, 3500 r×2.	0	0	Symptomfree 3 years.
♂	41	Palatum durum	Mixed t. fibromyxoepithel. Benign.	»	Roentgen, intraoral tube, 3500 r.	0	0	Symptomfree 2 years
♂	76	Gingiva	Basalioma, solid, semimalignant	»	Teleradium, 2 portals, 4190 r×2.	0	0	Symptomfree 3 years.

as recurrences of such benign tumors have always shown the same histological structure as primary tumors. The experiences made at the D. N. R. support decidedly AHLBOM's opinion.

The mixed character is an important feature, as the stroma in this group of tumors cannot exclusively be considered to be supporting tissue. It is evidently also of an autonomous character, as a development of purely sarcomatous pictures is seen now and then, where also the metastases show the same preponderance of connective tissue structures (THOMA & COLDMAN (11)). It is, however, advisable for the sake of classification to differentiate between the various types of tumors, whose histological peculiarities characterize the microscopic picture, but in by far the greater number of tumors within the main group, one will find traces of tissue structures which justify their classification into this group. Thus there is no reason to distinguish distinctly between tumors of a mainly mixed type and tumors of a mainly glandular or solid structure. The mixed type character is common for the whole tumor group from a histological point of view, as is the tumor localization from a clinical point of view. The designation »mixed» ought to be retained, at any rate until a basis of classification is found that is better than that offered by the purely morphological data.

The chief difficulty of the pathologist is to draw up the border between semimalignant and malignant mucous- and salivary gland tumors. AHLBOM discerns between these two groups on the basis of the following characteristics:

1. Semimalignant tumors:

a) completely encapsulated tumors, if they are:

1) cellular and little differentiated with sparse intercellular substance.

2) distinguished by cells which are atypical and polymorhous (hyperchromatic and polymorphous nuclei and mitoses).

3) Basaliomas with a structure suspicious of maligancy.

b) Tumors which present nodules outside the capsule or which have broken through the capsule but still show a tendency toward encapsulation.

2. Malignant tumors:

a) Those which have given rise to metastases.

b) Those which show infiltrative and destructive growth without the slightest tendency toward encapsulation.

The structural peculiarities of the mucous- and salivary gland tumors are characterized by a confused mixture of more or less distinct morphological pictures, showing a variable degree of differentiation, and in the

different areas of one and the same tumor the shape and the size of the cells may vary greatly. These cells are often both atypical and polymorphous according to the usual classification, but give in the benign forms of this type of tumors a certain typical pattern, that has nothing to do with biological malignity. Only an experienced tumor-pathologist can decide its exact place in this system of classification on the basis of the histological picture presented by such a tumor. This is done mainly on the basis of the mass, form and nuclear structure of the epithelial component. The claims to what can be termed infiltrative growth must also be much stricter than usual. The differentiation between semimalignant and malignant mucous- and salivary gland tumors is so difficult that the judgement of the patho-histologist will play a greater part than where other types of tumors are concerned, a relation which is seen on table no. 2, the number of semimalignant tumors at the D. N. R. being greater than the number in AHLBOM's material.

Previously in U. S. A. one has, broadly speaking, applied EWING's (12) classification: 1) benign adenoma, 2) adenocarcinoma (or carcinoma), 3) mixed tumor, which might also be of a basal cell cancer type (»adenoid cystic epithelioma»). F. STEWART (13) of Memorial Hospital, New York, discerns distinctly between truly mixed tumors and the other main group which is designated: adenocarcinoma. STEWART, however, points out that in most adenocarcinomas a tendency to a differentiation in the direction of mixed tumor could be demonstrated, but his tendency was often only slightly pronounced and consituted only a minor part of the picture.

In papers from the Mayo Clinic by NEW & CHILDREY (14), NEW & HALLBERG (15), MAYO & DOCKERLY (16), QUATTLEBAUM, DOCKERTY & MAYO (17), a different principle of classification, inspired by BRODERS, has been applied. Here the whole tumor group, inclusive of typically mixed tumors, is designated: adenocarcinoma.

1. Adenocarcinoma, mixed tumor type.
2. Adenocarcinoma, cylindroma type.
3. Adenocarcinoma, intermediate type.
4. Adenocarcinoma, miscellaneous type.

THOMA (18) discerns between »adenoid cystic epithelioma» (cylindroma) and basal cell tumors. However, there seems to be in U. S. A. also a tendency to differentiate the borderline cases into a special semimalignant group. Thus ACKERMANN & DEL REGATO (19) have recently proposed the following system of classification:

I) Benign

1) adenoma.
2) papillary cystadenoma lymphomatosum.

3) typical mixed tumor.
4) mucoepidermoid tumor.

II) Semimalignant (or of low malignancy)
1) mucoepidermoid tumor.
2) adenocarcinoma (cylindroma, basal cell c.).

III) Highly malignant
1) epidermoid carcinoma.
2) unclassified carcinoma.

IV) Sarcoma.

The designation adenocarcinoma, which in AHLBOM's system comprises a small and rare tumor group, an adenoma malignum, is in American literature far more comprehensive and seems to refer to the potential possibilities of the tumors for a malignant development rather than to their actual morphological picture, as when tumors of a mainly mixed type are designated adenocarcinomas. In our opinion the AHLBOM-REUTERWALL's principle of classification of mucous- and salivary gland tumors represents the hitherto best solution. The different tumor subgroups may here be classified comparatively easy, both as regards the clinical aspect and the histological pattern which is represented by the tumor concerned. In table no. 3 AHLBOM's (Radiumhemmet's) and

Table No. 2

Localization	AHLBOM	NEW & HALLBERG	WATSON	STOUT	MARTIN	D. N. R.
Hard palate	22	76	12	64	24	17
Soft palate	7		—			5
Buccal mucosa	6	46	5	—	—	3
Lips	2	15	1	18	—	1
Base of tongue	3	33	7	11	—	2
Floor of mouth	2	—	2		—	1
Oropharynx	5	61	1			3
Gingiva	—	—	—	—	5	1

D. N. R.'s materials of intraoral mucous- and salivary gland tumors — for the time being the only materials that have been subjected to an approximately uniform evaluation — are thus represented that the diagnoses of the tumor type and the classification of the different tumors with regard to the degree of malignancy, can be compared direct. It is seen on the table that there is, broadly speaking, good agreement between the two materials as regards the frequency of the different types of tu-

mors. There are minor deviations. Thus there is a greater number of basaliomas of a solid type in D. N. R.'s material, while in that of the Radiumhemmet there are more fibromyxoepithelial tumors. These deviations are certainly within the normal range of variation. The greatest difference is seen in the balance between semimalignant and malignant tumors.

The 33 intraoral mucous- and salivary gland tumors in D. N. R.'s material have been set up in table no. 1. in the possibly most surveyable form with specifications of sex, age, localization of tumor, tumor histology, therapy, recurrences, metastases and result of treatment of the patients.

Intraoral mucous- and salivary gland tumors apart from the large salivary glands were probably described for the first time by ROBIN in 1852. MALASSEZ (20) described in 1883 a tumor of the palate which he designated »krebsiges Zylindrom», but S. PAGET (21) was the first to demonstrate that tumors with the same histological structure as tumors of gl. Parotis, also occurred in the palate. Mucous- and salivary gland tumors from lips, basis linguae, mucous membrane of the cheek, soft and hard palate, processus alveolaris, oropharynx, larynx, trachea and bronchi, regio ethmoidalis and lacrimal glands, have been described more lately.

Table No. 3

Histological pattern	Benign	Semimalignant	Malignant
Mixed tumor, fibroepithelial	1 (0)	3 (1)	1 (9)
Mixed tumor, fibromyxoepithelial	1 (5)	4 (8)	1 (5)
Mixed tumor, fibromyxochondroepithelial	1 (0)	0 (0)	0 (0)
Basalioma, cylindromatous	0 (0)	10 (3)	2 (7)
Basalioma, solid	0 (0)	4 (0)	3 (2)
Slightly differentiated or undifferentiated epithelial tumor	0 (0)	0 (0)	1 (2)
Papillary cystic adenoma	0 (0)	1 (1)	0 (1)
Adenoma	0 (1)	0 (0)	0 (0)

The figures in parenthesis refer to AHLBOM's cases.

A number of major collections of materials of tumors of this group have been set up in table no. 2 in order to elucidate the frequency of occurrence of the different localizations. The localization of the 33 tumors in the material reported here will be seen from fig. 1.

Next to gl. parotis the palate is the region where mucous- and salivary gland tumors occur most frequently. In AHLBOM's material palate tumors constituted 9 % of the total material. They were more frequent than primary tumors in gl. submaxillaris and represented more than half

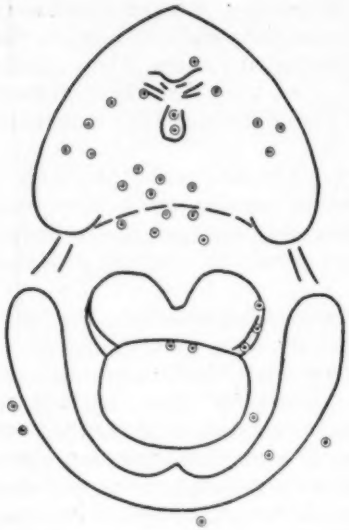


Fig. 1.

of the total number of palate tumors at the Radiumhemmet. Between 1932 and 1945 100 tumors of the palate in all were treated at the D. N. R. Out of these, 23 were of the mucous and salivary gland type, the others were epidermoid cell cancer. NEW & HALLBERG have found an almost equal number of mucous- and salivary gland tumors and epidermoid cell cancers in the palate, in AHLBOM's material there are mostly salivary gland tumors. Both AXHAUSEN (22) and GRIBEL (23) maintain that salivary gland tumors with localization in the palate are more frequent than the epidermoid cell carcinomas. MARTIN has found a greater number of epidermoid carcinomas, and in D. N. R.'s materials there are, as mentioned before, almost 3 times as many epidermoid carcinomas as mucous- and salivary gland tumors. This is undoubtedly due to the fact that in the said material there is a considerable number of women with epidermoid carcinoma in the palate, produced on the basis of irritation by dental prostheses (HOBÆK 24).

Since S. PAGET published his material consisting of 31 mixed tumors in the palate, major materials have more recently been treated by EISENMENGER (25), VOLKMANN (26), BOENNINGHAUS (27), AXHAUSEN, NEW & CHILDREY, AHLBOM, WATSON (28), NEW & HALLBERG, MARTIN and STOUT (29). A number of single reports and minor materials, by among others, WIRTH (30), GRIBEL, THOMA, RINGERTZ (31), BAUER & FOX (32), STIEBERT (33), HILL (34) and SHARNOFF & LISA (35), also bear witness of the frequency of these palate tumors.

Mucous- and salivary gland tumors are found more frequently in the hard than in the soft palate (cp. table 2, and Fig. 1) and, as a rule, in the posterior part of the hard palate, where the mucous glands are most numerous. NEW & HALLBERG found that most of them developed in the zone between the hard and the soft palate. In D. N. R.'s material 12 basaliomas were found in the hard and soft palate, 9 out of these were cylindromatous and 3 solid. In this region there were further found 3 typically mixed tumors, 1 papillary cystic adenoma and 1 slightly differentiated epithelial tumor. AHLBOM found as many as 16 mixed tumors, 7 basaliomas with cylindromatous features and 2 undifferentiated epi-

thelial tumors. In both materials the greater number were semimalignant and malignant tumors. Thus basaliomas are frequent tumors in the palate. Basaliomas with a cylindromatous structure are, as far as can be judged, considered frequent palate tumors also in American literature.

By far the greater number of mucous- and salivary gland tumors in the lips have been localized to the upper lip. ROHKAMM (36), in 1922, collected 27, and EGGERS (37), in 1932, 64 such tumors from the literature. About half of the cases collected by EGGERS were mixed tumors with chondroid tissue, the same has been demonstrated by BERNIER (38). From table 2 is seen that lip tumors are comparatively frequent in NEW & HALLBERG's and STOUT's materials, but, generally speaking, the lips are among the rarest localizations of mucous- and salivary gland tumors.

Several authors have been of the opinion that mucous- and salivary gland tumors in the buccal mucosa have developed from the molar glands. They are found in AHLBOM's and D. N. R's material somewhat more frequently than lip tumors, but must on the whole be considered rare, particularly as compared with the far more frequent epidermoid carcinomas in this region. FRANSSEN (39) has collected 7 cases, and in the large material of the Mayo Clinics there are as many as 46 cases (NEW & HALLBERG).

Basis linguae is also among the less frequent localizations of mucous- and salivary gland tumors. BRUNSCHWIG (40) has examined the literature up to 1929 and described 11 cases. EWING and QUICK (41) mention »adenoid cystic epithelioma» as typical of this localization. PACK & LE FEVRE (42) have reported 17 cases from Memorial Hospital, New York, and NEW & HALLBERG have described 35 cases from the Mayo Clinic. Most of the mucous- and salivary gland tumors in basis linguae are of the basal-cell type, but mixed tumors occur. One of the 2 tumors in D. N. R.'s material were fibromyxoepithelial, semimalignant.

Oropharynx (the palatal arches, and the tonsillar niches) are comparatively rare sites of the mucous- and salivary gland tumors. 6 out of the 82 tonsillar tumors described by BERVEN (43) belong to this group of tumors. According to NEW & HALLBERG 61 »adenocarcinomas» in basis linguae, against 76 in the palate, have been treated at the Mayo Clinic. This is a strikingly high number seen in relation to WATSON's & STOUT's numbers. In AHLBOM's and D. N. R's material the relation between mucous- and salivary gland tumors in oropharynx and the palate is as 1 to 6.

Mucous- and salivary gland tumors in the floor of the mouth (sublingual region) are evidently very rare. WATSON has reported 2 cases. AHLBOM has also 2 cases in his material. One case, which was observed at the D. N. R., was a fibromyxoepithelial tumor of semi-

Fig. 2.

Fig. 3.

malignant nature, undoubtedly with no connection whatever with gl. sublingualis.

MARTIN (44) has found 5 cases of salivary gland tumors in gingiva. There is one case in D. N. R's material, and 1 case has been reported by LOEB (45). The localization to gingiva is, to all appearance, the least frequent one.

The clinical diagnosis of intraoral and mucous-salivary gland tumors offer only seldom difficulties, particularly not in the palate. The tumor is, as a rule, small, from the size of a hazel-nut to the size of a walnut, but may be considerably larger (Fig. 2). The surface is, as a rule, smooth, and the tumor is often strongly projecting. The semimalignant and malignant tumors may be more flat and attached to the underlying structures on a broader basis. They are also completely or partly fixed. The consistency is from firmly elastic to hard. The mucous membrane covering the tumor, is generally without any changes. AXHAUSEN (46) points out that tumors of the basal-cell type in the palate have often a bluish hue. Ulcerations are, however, by far not infrequent in malignant tumors. Thus 7 of the malignant tumors in D. N. R.'s material were ulcerating. Mucous- and salivary gland tumors are only infrequently localized near the middle of the palate, but in that case they may be mistaken for a torus palatinus (Fig. 3). Semimalignant and malignant palate tumors sometimes produce roentgenologically demonstrable changes in the bone of the hard palate as a decrease in density to larger excavations. This was demonstrated in D. N. R.'s material in 11 out of 22 palate tumors, and as frequently for semimalignant as for malignant tumors. Thus this relation cannot be explained by tumor infiltration of the bone only, as the cause may just as frequently be one of pressure atrophy produced by an expanding in-

apsulated tumor. Naturally, biopsy ought to be undertaken in all cases f intraoral tumor. This is particularly the case in mucous- and salivary land tumors, where the determination of the histological type is of great herapeutic importance.

Malignant mucous- and salivary gland tumors metastasize more frequently than has hitherto been assumed. Metastases to local lymph nodes ave been histologically demonstrated in two cases, and palpable, not erified glandular metastasis in one case of D. N. R.'s material. Metastases ave been suspected in several other cases, where the patient, owing to eak health and often long and tedious travelling, has not been able to go to hospital for control, Out of 47 patients in AHLBOM's material, 12 had metastases, likewise 13 out of 76 in NEW & HALLBERG's and 10 out of 32 in WATSON's materials. Distant metastases occur late in the course of the disease and are frequently localized to the lungs, pleura and the bone system.

It is well known that mucous- and salivary gland tumors show a rather marked tendency to recurrences. GRIBEL maintains that 20 % of all salivary gland tumors recur. There were 9 recurrent tumors in AHLBOM's tumor material. 5 of these were mixed tumors, 2 basaliomas, cylindromatous, and 1 slightly differentiated epithelial tumor. In D. N. R.'s material there are 7 recurrences, 3 of these are basaliomas, predominantly solid, 2 basaliomas, cylindromatous, and 1 slightly differentiated epithelial tumor. Thus the intraoral mucous- and salivary gland tumors show as great a recurrence tendency as tumors in the large salivary glands.

In most clinics all over the world the treatment of mucous- and salivary gland tumors is surgical with subsequent radiotherapy, although this particular form of tumor has long been reckoned among the relatively radio-resistent tumors. This opinion is still held. Thus MARTIN pronounces, in 1942, that operable mucous- and salivary gland tumors, whether benign or malignant, need neither pre-operative nor post-operative radiological treatment, when the tumor has been removed, on the ground that radiation cannot be of any use, and only tend to delay the healing of the wound. QUICK & JOHNSON (47), SCHREINER & MATTICK (48) and NEW & CHILDREY had favourable experience about roentgen treatment of inoperable mucous- and salivary gland tumors. Also EWING (49), SPIES (50) and BACLESSE (51) a. o., have found that these tumors, particularly those of a basaliomous type, show considerable radio-sensibility in spite of their relatively little pronounced malignancy. AHLBOM's material also shows that of the really mixed tumors, those of a mainly fibro-epithelial type in semimalignant or malignant form, were moderate to very sensible to radio-therapy, while the other mixed tumors showed a more pronounced radioresistance. Papillary cystic adenoma and basa-

Fig. 4.

Fig. 5.

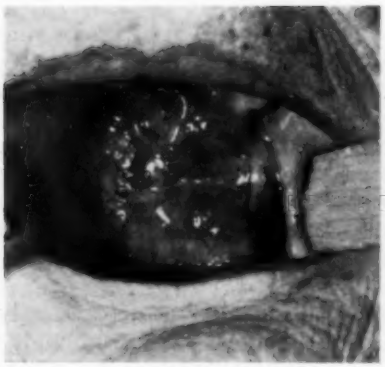


Fig. 6.

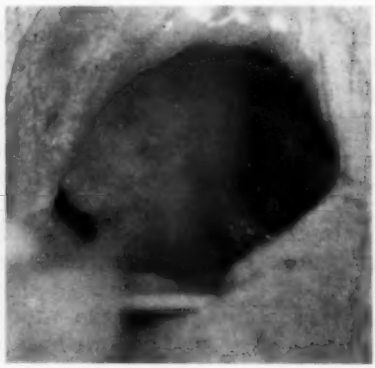
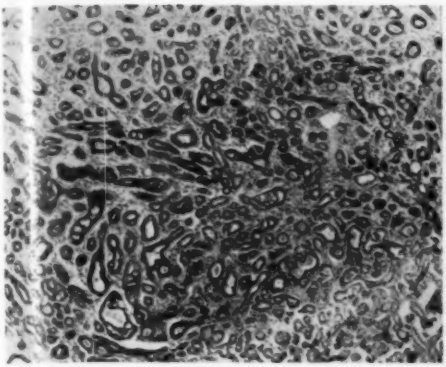


Fig. 7.

liomas with cylindromatous or solid features were also radiosensible to quite a considerable degree, while slightly differentiated epithelial tumors were moderately sensible. Tumors of the epidermoid cell cancer type, however, were often rather markedly radio-resistant.

BULL ENGELSTAD (52) has emphasized the radiosensibility of the tracheal salivary gland tumors. NEW & HALLBERG have found in patients who have received radiological treatment, 43% free of recurrences after 5 years and 25 % free of recurrences after 10 years. 13 patients in D. N. R.'s material have received exclusively radiological treatment, either because the tumor has been inoperable, or because, after the histological diagnosis, it has been considered so radio-sensible that there has been reason to believe that radiological treatment alone would be sufficient. 5 of these patients died, one of them 6 years after the conclusion of the treatment



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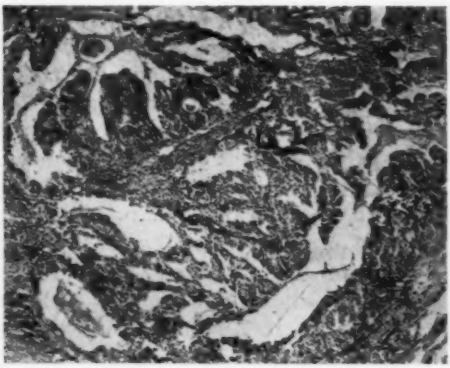

Fig. 11. Papillary cystic Adenoma.

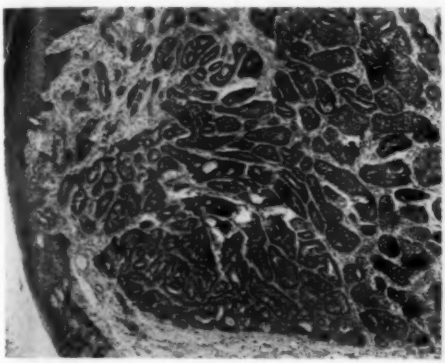

Fig. 9.

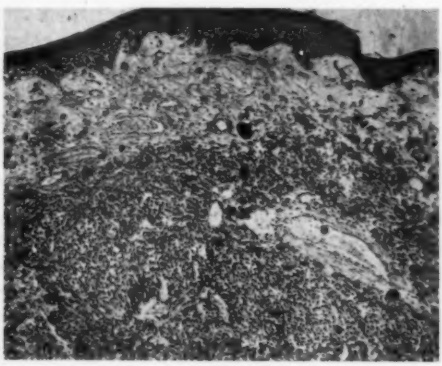

Fig. 12. Basalioma, solid.

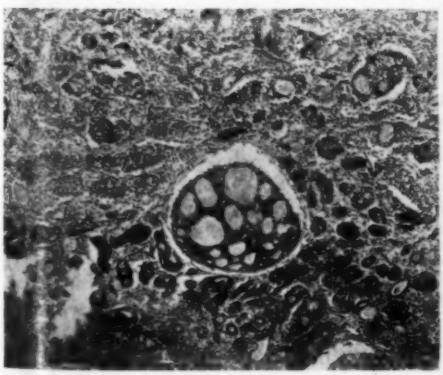

Fig. 10.

Figs. 8, 9 and 10. Various types of Basalioma, cylindromatous.

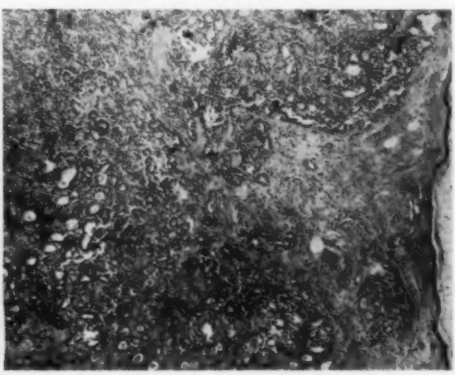

Fig. 13. Mixed tumor, fibromyxoepithelial.

without any sign of recurrences, the remaining 4 died from tumor from 8 months to 8 years after conclusion of treatment. 2 patients are alive with recurrences or tumor treatments. 5 patients are free of recurrences, 3 of them after 2 years, 1 after 3 years, 1 after 5 years and 1 after 10 years of observation. In the group that has been treated both operatively and radiologically and which comprises 20 patients, 4 died, three of them from tumor and one from intercurrent disease after 10 years. 1 patient is alive with tumor remnant, 7 patients are free of recurrences after 2 years of observation, 5 after a period of observation of 5 years, and 3 after 10 years of observation. Freedom of recurrences has been attained through purely radiological therapy in 2 basaliomas, cylindromatous and semimalignant, in 2 solid basaliomas, one semimalignant and one malignant, and in one fibromyxoepithelial mixed tumor of semimalignant nature. It is a general experience that the best therapy in cases of mucous- and salivary gland tumors, is the combined surgical-radiological therapy (radiosurgery), and it has given the best results also in the present material. But it is evident that in some cases a purely radiological treatment may suffice in semimalignant and malignant mucous- and salivary gland tumors. This is particularly the case with basaliomas of a cylindromatous or solid type. Indisputable conclusions, however, cannot be drawn from this little material, but the results show that radiotherapy alone can give patients with inoperable mucous- and salivary gland tumors a prolonged period of freedom of recurrence (fig. 4—5 and 6—7). Systematic preoperative radiotherapy has not been carried on at the D. N. R., especially because most of the patients have been operated upon before admission. Two inoperable palate tumors have become operable after radiotherapy.

It will be seen from table 1 that therapy at the D. N. R. has been administered partly as teleradium, partly in the form of roentgentherapy (ad mod. Coutard: 2 mm. Cu, 40—50 cm focus—skin distance, 175 kv., 4 m. a., with daily doses of 250 to 300 r. In some cases intraoral tubus has been applied). Previously, intratumoral radiotherapy or intraoral surface radium has partly been applied. The doses are represented on table 1. Additional treatment has been given in a number of cases with tumor remnants, or the treatment has been given for palliative purposes.

The semimalignant and malignant mucous- and salivary gland tumors have a comparatively favourable prognosis if the tumor is operable, and combined surgical radiological therapy is applied. The degree of malignancy of these tumors is moderate compared with other malignant tumors, and even in cases of inoperable tumors, it may take years before the patient dies from his illness. Metastases occur late, and usually first in the regional lymph nodes, later in the lungs and pleura or the bone system.

SUMMARY

After briefly mentioning the theories of the genesis of mucous- and salivary-gland tumors, the author deals with the generally applied principles of classification of these tumors, and points to The AHLBOM-REUTERWALL's principle of classification as the most useful one for the time being. 33 cases of intraoral mucous- and salivary-gland mixed tumors treated at the Norwegian Radium Hospital between 1932 and 1945 are briefly reported, mostly in tabular form with specification of site, histological type, radio-sensibility and tendency of recurrence and metastasis. The result of the treatment of these 33 tumors is presented, and the author emphasizes that although the combined surgical-radiological treatment is the therapy of choice, much can be attained in inoperable cases by radiological treatment alone.

ZUSAMMENFASSUNG

Nach einer kurzen Erwähnung der Theorien über die Genese von Schleimhaut- und Speicheldrüsentumoren, bespricht Verf. die bebrauchlichen Einteilungsprinzipien für diese Tumoren und weist auf das AHLBOM-REUTERWALL'sche Einteilungsprinzip als das z. Z. nützlichste hin. Über 33 Fälle von Mischtumoren der Mundhöhlenschleimhaut und der Speicheldrüsen, die zwischen 1932 und 1945 in der Norwegischen Radiumklinik behandelt wurden, wird kurz berichtet, hauptsächlich in Tabellenform mit Angabe ihrer Lokalisation, ihres histologischen Typus, ihrer Radiosensibilität, und ihrer Neigung zu Rückfällen und Metastasen. Verf. betont, dass, obwohl die kombinierte chirurgisch-radiologische Behandlung die Methode der Wahl darstellt, doch immerhin bei inoperablen Fällen mit radiologischer Behandlung allein viel gewonnen werden kann.

RÉSUMÉ

L'auteur mentionne d'abord, en passant, les théories sur la genèse des tumeurs des glandes muqueuses et salivaires, puis il s'occupe des principes généralement reconnus qui servent à les classer, et souligne que parmi eux celui dit d'AHLBOM-REUTERWALL est, à l'heure actuelle, le plus utile pour leur classification. 33 cas de tumeurs intrabuccales mixtes des glandes muqueuses et salivaires, traités à l'Hôpital Norvégien du Radium entre 1932 et 1945, sont succinctement rapportés, surtout sous forme de tableaux, en spécifiant leur emplacement, leur type histologique, leur radiosensibilité ainsi que leur tendance aux récidives et aux métastases. L'auteur présente les résultats du traitement de ces 33 néoplasmes et insiste sur le fait que, malgré que la combinaison de la chirurgie avec la radiothérapie soit la méthode d'élection, on peut beaucoup obtenir, dans les cas inopérables, par le seul traitement radiologique.

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